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PAEDIATRICS IN WESTERN NIGERIA

BY

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Introduction

The aim of this article is to present to the reader a broad view of the work of a general hospital in West Africa in its relation to the health of children. Facts and impressions were accumulated by the author during a year's sojourn in Nigeria, too short a time no doubt for a penetrating survey of local problems, but, possessed of the clinical potential of a flourishing and well-esteemed young hospital, long enough for a responsible survey of the main topics confronting workers in Child Health in West Africa. Practice in Africa is bewildering and refreshing to an English doctor, and requires a fresh approach adapted to experiences in new realms of pathology.

Several published descriptions have focused attention on the University College Hospital, Ibadan, during its growth (*vide British Medical Journal*, 1956). Now it is completed and possesses facilities that are unexcelled in tropical Africa. Built beside a teeming Nigerian city, a centre both of commerce and administration, and closely in contact with a university already of considerable renown, the new hospital is exceptionally favoured in its circumstances and associations.

In the waiting period while the new hospital was being built, the medical staff, who were already assembled, were occupied in creating a corporate hospital unit and at the same time in providing the local population of Ibadan with the fuller medical services that such an unexampled mustering of doctors and nurses made possible. These new facilities were grasped with alacrity, and in no sphere more willingly than by parents for their children. It was during this interregnum that the subject matter of this paper was collected. The base hospital was then the Adeoyo Hospital in the middle of the old town, a group of single storied buildings closely encircled by primitive dwelling houses, recently vacated by the Ibadan District Council to furnish the nidus of the University Hospital organization. The little renovation that was possible was done, and soon this primitive and unkempt small hospital became imbued with a mood of energy and promise, so that its achievements far over-reached its material restrictions. The children's ward consisted of a congested room with a balcony, together able to contain some 35 infants and children under 12 years of age. In this ward fulminating gastro-enteritis was treated beside broncho-pneumonia, septic ulcers beside extensive exposed burns, typhoid beside malaria and tuberculosis amidst them all. The frequency of cross infection can only be roughly guessed, but was certainly not very great, as instanced by the fact that diarrhoea seldom developed in hospital even in long-stay patients. Perhaps we owed this to the sunlight and free circulation of air in a ward with constantly open doors and windows. An element of squalor is inseparable from work in these circumstances, but the first affronted reaction to bed linen grey from use and re-use, to the one ward lavatory of hole-in-floor type which served for patients, staff and visitors, to the 'sluice room', a square cell with a tap and a hole in the wall from which the effluent flowed outside in a rather ill-defined way, and to the chicken which continued defiantly to inhabit the out-patient verandah, passed when one realized that these were unalterable but temporary conditions, and that ill results from them were so much less than might be imagined.

Social Aspects. Ibadan is the chief town of the Yoruba tribe by whom Western Nigeria is largely peopled. Easy-going, generous and intelligent, the Yorubas have constructed a community based upon peasant agriculture but centred upon towns. They live in urban concentrations often of considerable size, but for part of the year retire to their farms at a distance to work the land. Consequently there is a fluidity about the population, making census figures for an area inaccurate. Peasant society is largely polygamous and responsibility for wives and children is only partly borne by the husband, with the result that the women make themselves as far as possible economically independent by petty trading, for

which they possess enormous aptitude. Market stalls tended by blue-turbanned and vociferous womenfolk are a prime ingredient of Yoruba-land.

In Ibadan there are reputed to dwell some half a million people. It is a sprawling town of mud-built dwellings with corrugated iron roofs intermingled with substantial brick villas and modern emporia. It is fringed by a new growth of fine buildings in a modern tropical idiom, and by reservations of dwelling houses with extensive gardens. Open drains through the town convey sewage and stormwater. Ibadan streets at all times are a press of sound and life, thronged with pedestrians, bicycles and impatiently hooting motor traffic, a witness to the liveliness and vigour of its many-faceted society, which contains Indian, Lebanese and European communities as well as African.

Uncomprehending of the methods and beliefs of practitioners of Western medicine, the common people have, notwithstanding, been quick to recognize its capabilities, particularly since the advent of potent chemotherapeutic drugs. Attempts at rational exposition of the causes of disease and the aims of treatment encounter customs, fears, superstitions and taboos that among the illiterate are a complete bar to understanding. The following account of popular beliefs in Ibadan is based upon a recent article (Omololu, 1956). Diseases, Dr. Omololu says, are always caused by the wrath of spirits, by worms, or by the machination of enemies. Education modifies but does not efface this concept. The conception of micro-organisms causing disease has never been entertained in Yoruba-land. In a polygamous society the ground is fertile for suspicion and culprits are easily found. At a more advanced level, certain poorly-defined notions of pathology are used as comprehensive explanations of a wide range of disorders. A past history of urethral discharge, for example, is regarded as infallible evidence of gonorrhoea and may be held responsible for any urinary, joint or skin symptom. 'Black blood' may be regarded as the cause of an illness whose manifestations range from malaria to vitamin B deficiency and to impotence. A change of blood is indicated and a good doctor knows that injections rather than dietary advice or mixtures can best accomplish the change. It is well-known that injections are the most potent remedies available for almost anything.

Yoruba-land is extremely conscious of its gastro-intestinal tract and in consequence any symptom arising from it is presented forthwith. A patient might fail to mention that he has dyspnoea, but not that he has a coated tongue or that he has vomited. Diarrhoea, dysentery and piles are to the common people synonymous and may be used to denote anything from frequent stools to pruritus ani. One may never take it for granted that the patient has the slightest idea of the meaning of the word he is using; rather it is safer to assume that he is conscious of something amiss in a roughly specified region of the body. A person who complains of constipation for example cannot even be assumed not to have diarrhoea. Intestinal worms are almost omnipresent and the popular mind has conferred upon them an almost unlimited potential for evil. Any digestive upset, increased peristaltic movement, or irritation anywhere in skin or scalp is laid at their door.

The father is dominant in the Yoruba family and his availability and mood are important in deciding whether or not one of his children shall attend hospital. Whether he lives with the mother or not, his consent must be obtained before the child can be brought into hospital. If this is not done the wife by general consent can be divorced with ignominy. Generally speaking, in their devotion to their children, in their courage in breaking with the past, in their efforts to cooperate with doctors, whatever the difficulties, and in their uncomplaining tolerance of discomforts and delays, the young Nigerian mothers deserve measureless praise. For those better-educated girls, increasingly under the influence of English speaking cultures, who have made a monogamous marriage and are yet bonded by birth to a Yoruba manner of life, there is an intolerable conflict at every turn, especially in the raising of their children. A danger is that they will reject their heritage in favour of the meretricious attractions of suburban English culture.

Children are fed almost universally on the breast and lactation is a more abundant and more efficient process than in Britain, rarely attended by complications of engorgement or sore nipples. Manual expression of breast milk occasions no difficulty. At six months or after the output often decreases, and, as it is common to breast feed for one or two years, this is an important influence in retarding growth. Feeding at the breast is entirely on demand and the baby, slung in a girdle on his mother's back, is close enough to be sure that his needs are not overlooked (Fig. 1). Weaning, which occurs late, is likely to be to 'pap' (a paste of maize flour) with occasional meat soup (a dilute vegetable broth, not of much nutritive value, containing dried fish, peppers, palm oil and small quantities of meat). This diet is subsequently varied by the addition of yam and cassava, beans and plantains. Eggs and milk are not in the diet, nor are meat, fish or fresh fruit in any adequate

amount. Consequently symptoms of protein deficiency are wide-spread and are aggravated when early withdrawal from the breast is necessary or if illness makes extra demands upon metabolism. Tradition as much as economics is responsible for this ill-balanced diet, and striking benefits are seen if parents can be prevailed upon to give preference to naturally-occurring rich protein foods such as beans, dried fish, ground-nuts and guinea corn, rather than to the time-honoured starchy yams and cassava. The admission of children to hospital has some educative value here and it is hoped that parents will profit from hospital precept and admonishment in the subsequent management of their children (Fig. 2).

FIG. 1.—Carrying a baby.

FIG. 2.—Mother and child from infant welfare clinic.

On the whole the Yoruba peasantry is a clean people and standards of personal hygiene are good despite the fact that some methods of child care, such as the early management of the umbilical cord, seriously conflict with European ideas. The babies are mainly overdressed, except for diapers which are non-existent among the uneducated. No attempt is made to inculcate early control of sphincters, which seriously complicates sanitary arrangements for large out-patient clinics. Messes of all sorts are disposed of rapidly by Yoruba women, usually being wiped up by some article of their own clothing; failing that, lifted by hand and thrown to the ground outside.

The educated section of the community is bilingual, English being used for everyday communication. Among the illiterates, the main source of the hospital attenders, an ability to speak English is exceptional. The language problem is further complicated by numerous minority groups from other parts of Nigeria, who dwell in and around Ibadan. Yoruba is a difficult tonal language, requiring a flair to master it; a great part of the hospital work is carried on through interpreters. Although to work through an interpreter is probably less of a constraint in paediatrics, when histories are already at second hand, than in other branches of medicine, the intervention of a third mind is a great hindrance to speed and accuracy. Time-wasting confusion results from a search for detail, with the result that question and answer have to be reduced to rudimentary exchanges, paring away much that is valuable and that might facilitate diagnosis. Interpreters engaged in utilitarian repetitive conversations become desultory and inexact, or at worst provide the answers that they surmise the doctors are expecting. Sympathetic contact with the patients, so vital to indoctrination of novel ideas, is often a struggle to achieve and consultations can too easily become bleak and irritable under the twin pressures of haste and obscurity. Fortunately the strongly developed African sense of humour is often able to bridge the gap and to build an enduring bond of sympathy.

Statistics. The University College Hospital is a very busy one (Figs. 3, 4). If we take the month of August, 1956, at random, approximately 8,000 new out-patients attended the hospital and a quarter of these attended the paediatric department. In all, 23,000 out-patients came to the hospital during the month, and about 300 children attended daily. In the same month, 121 children were admitted to the 36 beds of the children's ward, as against 200 admissions to 131 adult medical and surgical beds in the hospital in the same period. There was therefore a relative preponderance of sick children.

During 1956, 1,881 children were admitted to the children's ward of Adeoyo Hospital. The diagnoses of these children are listed in Table 1, together with some figures concerning mortality. No less than 488 (26%) of these children died. There were approximately 300 more males than females in this series and the male death rate (24% contrasted with 28%) was rather lower than the female. The male preponderance was considerably accentuated in admissions for tetanus, and for diarrhoea at all ages, whereas a significant female preponderance was evident in admissions for protein malnutrition.

When discussing the age distribution of the patients it is important to remember that statements of age by parents are very inaccurate. Dealing as we are with large numbers it is probable that inaccuracies in the one direction are roughly

FIG. 3.—Outside the Children's Clinic.

FIG. 4.—Waiting their turn.

balanced by inaccuracies in the other, but the further one gets from birth, the more conjectural are the recorded ages. With this proviso, it appears that one half of the children were under 1 year old, one third between 1 and 3, and one fifth older than this. In this series the death rate according to age

TABLE 1

ADMISSIONS TO CHILDREN'S WARD, ADEOYO HOSPITAL, 1956, ANALYSED ACCORDING TO DIAGNOSIS, AND LISTED IN ORDER OF FREQUENCY

Diagnosis	Total Number	Deaths	Mortality (%)	Sex Ratio M : F
Pneumonia	309	111	36	1·1 to 1
Diarrhoea and vomiting	243	74	30	2·05 to 1
Anaemia	223	29	13	1·3 to 1
Protein malnutrition	157	54	35	0·89 to 1
Tuberculosis	113	33	30	1·3 to 1
Trauma (including burns)	104	7	7	1·3 to 1
Other alimentary disorders	102	12		
Tetanus	95	58	61	2·0 to 1
Other respiratory disease	82	8		
Protozoal and helminth infections	81	14		
Unexplained and unclassified illness	80	46	57	1·2 to 1
Infections of skin, lymph glands, and subcutaneous tissues	78	13		
Other acute specific infections	69	19	28	0·94 to 1
Diseases of nervous system	53	9		
Diseases of genito-urinary system	44	10		
Diseases of bones and joints	38	1		
Purulent meningitis	36	13	36	1·06 to 1
Tumours	31	4		
Other nutritional and deficiency diseases	24	3		
Cardiac and circulatory disease	23	8		
Neonatal diseases	17	7		
Diseases of liver	13	2		
Diseases of eyes	11	2		
Poisoning and idiosyncrasy to drugs	9	3		
Other blood disorders	8	3		
Diseases of endocrine system	2	0		
Total (after correction for multiple diagnoses)	1,881	488	26	1·36 to 1
Total males	1,090	265	24·5	1·17 to 1
Total females	791	223	28·5	

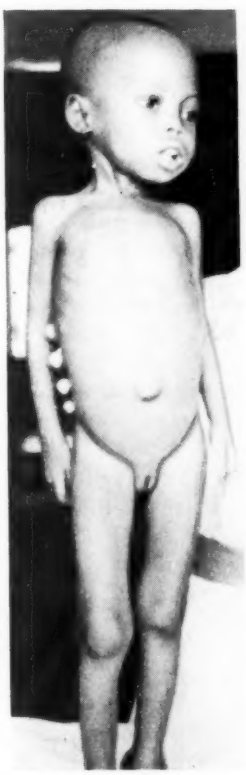
remained constant at 30% up to 6 years, and after that fell steeply. Just over one half of the total deaths occurred in infants (i.e. less than 1 year old).

Selection of Cases for Admission. Children were admitted nearly always for treatment, seldom for investigation only. A strict criterion was that, irrespective of diagnosis, the treatment could not be given as an out-patient. Priority was given to the desperately ill and to acute surgical emergencies. A few children from the surgical waiting list were admitted each week and a few others by the ophthalmic surgeon, gynaecologist and dermatologist from their clinics. The proportion of infants to older children was regulated to some extent by the number of infant cots available. The upper age limit was about 12 years, but was determined also by whether or not the child was too tall to lie comfortably in a small bed. Less direct influences were the willingness or otherwise of parents to accept admission (few in fact refused), and the reputation of the hospital for treatment of particular clinical entities. In general, where it is plain that treatment of a condition is effective, patients will come. The converse is also true. Geographical factors change the emphasis on certain diagnoses; Ibadan has a reputation as a healthy district, and the incidence of many diseases is undoubtedly greater elsewhere in Nigeria. On the other hand, community diseases such as tuberculosis and gastro-enteritis may be unduly common in this huge congested township.

Examination of Patients. For the practitioner accustomed to fair-skinned children there is much to learn about the interpretation of physical signs of illness in Africans. Assessment of mucosal colour, jaundice, skin disorders, intelligence and indeed the recognition of an ill child all require experience. At first, judgment of a child's age is often at fault by as much as 3 years. Heights and weights grossly beneath the normal for the chronological age are very common (Fig. 5). Walters (1956) found that children in Ilobi, a village in South West Nigeria, were some 10% shorter in height than English children and that over the first 5 years of life they were about 20% lighter in weight. Racial differences in physique play a part in this, but undoubtedly more important in keeping the children back are undernutrition and ill-health. Children attending out-patients for example might have weights of 15 lb. or even less at the age of 3 or 4.

Many African children, of course, especially those from better homes, are at every age physically comparable with European, and it is perhaps just this spread from super-normality to the most remarkable physical retardation that makes age assessment so difficult. Newly born babies are also small, with birth weights averaging 1 lb. or so below what is customary in England. Their range of skin colour is very great, and includes a shade of yellow-brown difficult to distinguish from a rather deep neonatal jaundice. Certain common symptoms of childhood carry different implications in Nigeria from those they have in Britain. Pallor for example is likely to be due to malaria or to sickle cell anaemia, oedema to protein malnutrition or nephrosis, abdominal pain to dysentery or ascariasis, jaundice in the newborn baby to septicaemia, and in the older child to a crisis of sickle cell disease, while convulsions, one of the commonest reasons for seeking help, are much more ominous than they are here. In the respiratory field alone is the range of diagnoses closely comparable to that in England. An enormous morbidity from whooping cough, bronchopneumonia and tuberculosis is common to the children of both countries.

The death rate in the children's wards is horrifying by European standards and exceeds the total of deaths in all other departments of the hospital.



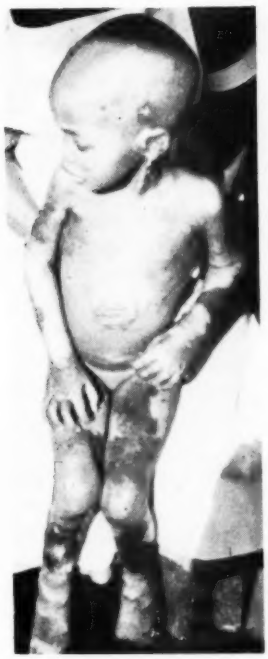


FIG. 6.—Skin changes in protein malnutrition.

FIG. 5.—Five-year-old child.

The greater number of deaths occur within 24 hours of admission, and malnutrition, gastro-enteritis, broncho-pneumonia and tuberculosis account for most of them.

Clinical Discussion

There follows a commentary upon the illnesses that were encountered. They are considered under the headings, and in the sequence, of Table 1.

Pneumonia. This was the commonest reason for admission to hospital and was the greatest single cause of death in the whole series. Two thirds of the cases were in infants, and of the remainder most were in the 1 to 3 year age group. Among the latter, the mortality was even higher than in infants, probably because this is also the age group of protein malnutrition. A bacteriological diagnosis was not often made, but most cases were believed to be broncho-pneumonia of the usual catarrhal origin. Staphylococcal aetiology was inferred on several occasions because of the radiographic appearances. A short fulminating illness, often accompanied by diarrhoea, was the most common mode. Some of the patients in whom the illness ran a more protracted course may have been suffering from whooping cough. The prevalent local method of force-feeding weakly babies by hand certainly accounted for some aspiration pneumonias. Convulsions were always of serious prognosis; they were not obviously due to oxygen lack, and meningeal infection was always excluded. A better clinical response to one antibiotic rather than another was not demonstrated, and the most frequent treatment was with penicillin and streptomycin combined. Two cases were mongols.

Very many cases of pneumonia were treated as out-patients, and because they were less severe the outlook was much more favourable. Those admitted to hospital were either suffering from a virulent infection or were in such a bad condition that they could not stand even a moderate illness.

Diarrhoea and Vomiting. Two thirds of these were infants, and about a quarter of them died. Many were admitted in an extremely dehydrated state. Gastro-enteritis following upon prolonged underfeeding frequently provided us with an emaciated child to whom diarrhoea was the last straw. Nevertheless, one cannot feel content with the results of hospital management of gastro-enteritis. The diarrhoea itself usually ceased fairly quickly with the usually accepted regime of parenteral fluids and chemotherapy. Electrolyte disturbances were corrected, but in many cases the child remained gravely ill and perished on the third or fourth day at a time when hydration was adequate and the known biochemical disturbances had been fully corrected. Much thought was given to the reason for these failures, and vitamin deficiency, hypocalcaemia, adrenal failure and hypoglycaemia were all excluded after experiment. Profound cerebral effects seemed to follow dehydration in many of these babies, who would have convulsions and subsequently remain in a blank immobile state with alteration in muscle tone and a tendency to muscle twitching which was ominous and not properly understood. Lumbar puncture was unrevealing. A number suffered from tetany during the recovery phase, and when tested, the serum calcium was found in such cases to be low. Pathogenic organisms were scarcely ever isolated from the stools, and the bacteriology of infantile gastro-enteritis in Nigeria has not yet been properly classified. As already remarked there was a striking preponderance of males among these patients.

Diarrhoea is probably the commonest symptom with which a young child is brought to hospital. Most out-patients were not very ill, and could be quickly restored by simple treatment, in practice usually a kaolin mixture and an anti-malarial drug. The majority were probably in fact symptomatic diarrhoeas, and not true enteric infections. Others, of course, were suffering from protein malnutrition, and usually revealed themselves as such by their failure to improve and by other signs. True bacillary dysentery was not uncommon in out-patients and responded so well to sulphonamides that such cases seldom got into hospital.

Anaemia. The infants in this group were usually suffering from some respiratory or alimentary illness, and were discovered because of their extreme pallor. Babies with haemoglobin levels of from 10% to 40% were admitted and transfused. They did very well, spending only one night in hospital in most cases, and seldom seemed to require further replenishment. The nature of the anaemia is unsolved. Dr. R. Hendrickse has studied these Ibadan babies with particular attention, and is of the opinion that in most of them the anaemia is due to the effects of malaria. It is doubtful if it is due to haemolysis alone, and there must be an individual idiosyncrasy as these cases were random among infants in the same environment and exposed to the same risk. Their nutritional state seemed irrelevant. The anaemia was usually normochromic, and iron deficiency, although it was not

excluded by serum iron levels, is probably not an important contributory agent. Most were less than 6 months old. Dr. Hendrickse found that some of them could be made to reconstitute their own haemoglobin without transfusion, if they were given anti-malarial drugs only. Combination with broncho-pneumonia was common and accounted for some of the deaths. Others died because their anaemia was too profound to be treated in time, and one or two died of the cardio-vascular effects of transfusion.

In older children the aetiology was mixed: iron deficiency, post-infective anaemia, malarial anaemia and no doubt certain cases of sickle cell anaemia, although we have tried to classify these separately. As already mentioned, protein malnutrition does not seem to be a cause of profound anaemia in this population.

No less than 53 cases of sickle cell anaemia were admitted during the year. They were fairly evenly scattered in age throughout childhood. Most of them were admitted in crisis, that is to say with a low haemoglobin, fever and a tinge of jaundice, and with pain or even swelling around the joints. The blood often showed a high leucocytosis with a high nucleated red cell count. The spleen was large and sometimes tender. The swellings around the bones were sometimes inflammatory and this was especially true of the spindle-shaped swellings of the fingers and toes from which pus due to a salmonella organism was sometimes extracted. Jaundice seemingly of an obstructive type occurred in a number of these children, most probably due to a hepatitis. The diagnosis of sickle cell anaemia was confirmed by finding in the laboratory sickling of all red cells within 24 hours, accompanied by a filamentous form of red cell distortion. More accurate diagnosis was obtained by electrophoretic identification of the haemoglobin. There was further support for the diagnosis in the skull contour and in characteristic x-ray alterations in the trabeculation of the bones, although these signs were not invariable. A family history was also helpful. In Western Nigeria the incidence of sickle cell trait is 24%, while sickle cell anaemia occurs in 0·3%. The combination of sickle cell haemoglobin and haemoglobin C occurs in 1%.

We performed Tallquist haemoglobin estimations whenever children seemed unduly pale. Much anaemia of intermediate severity was treated empirically with chloroquine and iron, and a response could be obtained in most cases. In Ilobi, Walters (1956) found haemoglobin averages of 9·2 g.% in the 0 to 1 year age-group, and of 10 to 11 g.% in the 2 to 9 year age-group.

Protein Malnutrition. Although this figured only as the fourth commonest reason for admission, it was in many ways the most important disorder that we were called upon to treat because of its high mortality and its extreme prevalence in less severe forms, and also because it is preventable. The peak period for the disturbance is between 1 and 3 years, and more than half our in-patient examples fell into this age-group. A quarter of them were between 3 and 6, and only 14 were under 1 year old. After 6 years the incidence fell away sharply. The older children showed a slightly higher death rate, and at all ages a preponderance of females was noticed and this was not explained. Protein malnutrition formed a backcloth to all the illness we treated during the year; minor evidence of it was continually noted, and it was not used as a primary diagnosis unless the disease was gross. Even among this group, accompanying diseases figured largely. Pneumonia, tuberculosis, diarrhoea, anaemia and sepsis were the most important of these.

Early manifestations of the disease were oedema of the feet, and lassitude and fretfulness with some diarrhoea. Changes in the pigmentation of the skin came next (Fig. 6), and an extension of oedema. There might be some discolouration of the hair. In bad cases there was gross generalized oedema tending to spare the serous cavities, and a typical mosaic dermatosis on the limbs.

Some other bad cases were miserably emaciated with trophic skin changes but without oedema. In every case there were the characteristic hypoproteinaemia and dietary history as confirmatory points. Persistent watery diarrhoea, common to nearly all cases, aggravated their ill-health. Anaemia, though sometimes gross, did not seem to be a constant symptom, and a haemoglobin level of about 60% was average. These were most unpredictable children to treat, many dying suddenly during the first week in hospital. There would often be no warning of this, and one would be surprised to find that a child who was apparently improving had died during the night. There was a particular tendency to die within the first 48 hours after admission, which seemed greater than could be accounted for by the fact that these children were brought to hospital only when they were in an advanced stage of the disease. Treatment consisted of a graduated introduction of high-protein milk; graduated because too early feeding with concentrated protein exaggerated the diarrhoea and worsened the condition. Nevertheless, we have wondered if the abrupt change from their native high carbohydrate diet to this thin, semi-fluid one played a part in the early death of some of these

cases. Education of parents in the best use of available foods was also a vital part of treatment.

Those who did not die improved quite rapidly and had a diuresis at about the end of the first week, and there was subsequent weight gain and restoration of vigour. Many were able to go home at the end of the second week, and were followed up at a Nutrition Clinic. The importance of routine radiographs of the chest in these cases came to be recognized because many of them, even though infected with tuberculosis, failed to give a positive tuberculin reaction in their malnourished, anergic state.

Tuberculosis. Tuberculosis is the commonest reason for admission of patients to the adult medical wards, but only comes fifth in frequency in children. It is, nevertheless, a serious and important disease, as witnessed by the 113 cases who were admitted during 1956. Pulmonary primary infection was, of course, far and away the commonest manifestation, and the brunt of the severe infections fell on young children. There were 17 cases of tuberculous broncho-pneumonia and four cases of miliary tuberculosis among this group. An association with protein malnutrition was common, and the two diseases together are a serious hazard to life. Tuberculous pleural effusion does not seem to be very common, and only two in hospital (and two other out-patients) developed this complication. There were three cases of tuberculous pericarditis with effusion, and one of tuberculous polyserositis. Abdominal tuberculosis, mainly the ascitic form of peritonitis, contributed 10 cases, and one of these showed a pseudo-chylous effusion.

Meningeal tuberculosis seemed to affect a lower age-group than is customary in the United Kingdom. Half of the cases were under 1 year old. Our cases of meningitis did very badly in spite of the use of all forms of chemotherapy, and in many cases cortisone as well.

It is a clinical impression that the glandular element of the primary complex within the chest assumes larger proportions than with English children. Very considerably broadened mediastina were common, but parenchymatous infiltration in the lung was frequently inconspicuous.

Tuberculous superficial lymphadenitis did not account for many admissions, but we noticed a proneness to large axillary tuberculous buboes, apparently not due to a superficial skin focus in the affected limb; in fact many had co-existing disease in the chest. Superficial tuberculosis seems very uncommon, which is the reverse of what one would expect, seeing that so many children have skin sores, and so many adults have open tuberculosis.

In considering tuberculous bone disease one notices at once the remarkable preponderance of Pott's disease of the spine. This accounts for the majority of tuberculous bone lesions at all ages, and begins sometimes in infancy. Spinal caries admitted to hospital had nervous complications as a rule. In such cases, costo-transversectomy with evacuation of paraspinal abscesses was often performed. The prognosis for return of nervous function below the site of disease was quite good in reasonably early cases, though some paraplegia proved irreversible. The policy adopted by Mr. P. Konstam, who was in charge of the surgical management of most of them, consisted in partially immobilizing the spine in a plaster of paris jacket and then treating the child as an ambulant out-patient, unless nervous complications were present. At the same time, of course, the child received chemotherapy. The results of this regime are to be the subject of a report by Mr. Konstam, but it may be said that these simple measures have been rewarded with striking success, and that firm healing with abundant perispinal calcification is achieved in a comparatively short time. Isolated cases of tuberculous hip or knee disease were seen, but were not common.

In a seven-month period, August, 1956 to February, 1957, 253 new children were referred to the weekly tuberculosis clinic. Of these 158 were deemed to have active tuberculosis. A number of other children who were referred to a surgical tuberculosis clinic with glandular or bone lesions, have escaped this inventory. Post-primary lung lesions were present in 11. Phlyctenular conjunctivitis seems to be a common addition to the tuberculous picture, and once established the tendency to reactivation with intercurrent infections persists for a long time. A good deal of corneal damage in children is caused in this way. On the other hand erythema nodosum was seen only twice in the year. Suspicion of a false positive Heaf test was created in five cases, all in very young children in whom after considerable observation no evidence of tuberculosis infection past or present could be found. The Heaf test in each case was positive Grade I. Non-specific tuberculin reactions have been discovered as causing confusion in the Heaf testing of African children, and the subject is discussed by Henshaw (1955).

If disease of the same severity is compared, these Nigerian children with tuberculosis appeared to progress under treatment at least as well as English children. Out-patient chemotherapy was used for all cases of primary tuberculosis with symptoms. Streptomycin was reserved for the more seriously

ill, so that P.A.S. and isoniazid were given to the majority. It was gratifying to see the rapid reduction in toxaemia, and the gain in weight. Conditions were such that investigation of contacts could not be carried out.

We carried out a small study of children attending the general out-patients at the Adeoyo Hospital. New cases were Heaf tested on their first attendance and the result read three days later. Results were only obtained on 350 children. The proportion of Heaf positives was as follows:

Age (years)	%
Under 1	4
1–3	14
3–6	23
Over 6	53

These were of course ailing children and a highly selected group, but the sample affords some indication of the level of primary infection in the Ibadan population.

Trauma. Burns and scalds, the most important diagnosis under this heading, made a considerable contribution to the work of the children's ward. The 47 cases in the year were evenly distributed over the ages up to 6 years; there were few after that. Most occurred around the domestic hearth, from clothing catching alight or more often from scalding fluids falling upon the children. A small group was due to a local method of reviving cases of convulsions by hot applications to the feet. Management of burns in the open ward might be expected to lead to serious cross-infection, but in fact this was not so. They were treated by the open exposure method and early skin grafting was carried out where necessary. The incidence of complications was surprisingly low, undoubtedly lower than it would be in an open ward in the United Kingdom. In part this may be due to the rarity of the streptococcus. Blood transfusions were necessary for many of these children, and all of them were nursed under mosquito netting to keep off flies. Four died, a mortality of 8%. Some remained in hospital for relatively long periods of six to eight weeks.

Other Alimentary Disorders. Between 1 and 6 years of age many Ibadan children suffered from cancrum oris. The disease starts as a marginal gingivitis with bleeding gums, after which infection encroaches upon the bony alveolus. A destructive osteomyelitis of the jaw begins and the infection then spreads outwards from this area to contiguous soft tissues, which are eroded. Within a matter of a few weeks there may be a large necrotic area which continues to extend until checked by treatment. The process responds very sensitively to penicillin and extension ceases as soon as this treatment is begun. Nevertheless, a long time is necessary for separation of the dead tissues, which may include a large bony sequestrum, as well as soft tissues sometimes composing the whole thickness of the lip or cheek. Great deformity arises therefore in some children who have been treated for severe cancrum oris, and the plastic repair of this is formidable. Most of the children with cancrum are in a state of reduced nutrition and may be anaemic, but the process itself does not seem to cause much, if any, general illness. In out-patients many children are seen with the premonitory symptoms of cancrum oris, namely bleeding gums, foetor oris and marginal gingivitis, and these symptoms can be brought to an end quickly with a few procaine penicillin injections.

A common surgical condition is intussusception, which in Nigeria mainly affects boys aged from 3 to 10 years. The symptoms are those of subacute intestinal obstruction and it is readily diagnosed and corrected.

Among other conditions that call for comment were five cases of Hirschsprung's disease. This disorder is evidently one that must be taken account of in Nigeria. On the other hand congenital intestinal atresia was only seen twice. Several cases of partial aplasia of the abdominal musculature, without renal abnormality, were seen and may be related in cause to exomphalos, which was observed to be one of the commoner congenital malformations, and to umbilical hernia which is very prevalent indeed. During the year, there was only one case of appendicitis in a child and no case of congenital pyloric stenosis.

Tetanus. Tetanus was the third greatest cause of death in children in this hospital series. In the adult medical wards this disease is the chief cause of death by a considerable margin. Neonatal tetanus comprised two thirds of our total cases. A very large number of infants born in hospital go home within a few hours, and are therefore submitted to the same methods of cord dressing during the early days of life as befalls those born at home. Nevertheless none of our babies with tetanus were born in hospital, and this suggests that liability to this disease depends upon the way in which the cord is severed at birth, and not upon the applications subsequently used. The mortality in newborn babies with tetanus was 77%. Mortality rates are closely related to the day of life on which the first symptoms develop (Fig. 7).

Various regimes of treatment for the newborn were tried through the year, some elaborate, some fairly simple. We still seek a simple routine of universal application which does not require exacting nursing or vigilant medical observation. Most of the deaths occurred after the first few days, the infant entering upon a cold, inanimate, oedematous state with shallow respirations. Another mode of dying occurred during the third week, with a high swinging temperature and finally hyperpyrexia.

Only a quarter of older children with tetanus died, and the risk of death became progressively less with increasing age, up to adolescence. It was often difficult to decide upon the site of entry of the tetanus organism. Chronic otorrhoea was several times suspected to have given access to tetanus.

Active immunization of the population has not been started. Anti-tetanic serum is used routinely in out-patients for wounds and abrasions. We saw a death in a child from anaphylaxis after this.

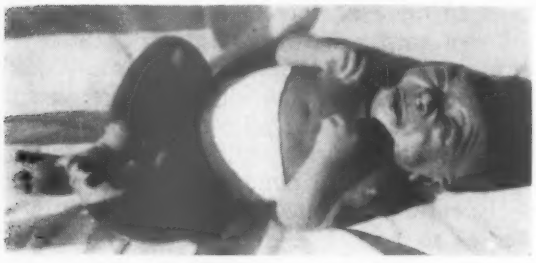


FIG. 7.—Neonatal tetanus.

Other Respiratory Disease. Retropharyngeal abscess was a condition of which we had to be continually mindful; there were seven cases in the year. Another interesting entity was a hyper-acute pharyngitis with a plentiful soft yellow exudate, grave toxaemia and pronounced cervical adenitis with neck swelling. Although these cases (of which we had three, all of whom died) so closely resembled diphtheria, this organism was not isolated from any, nor in fact was any organism incriminated. In one, exudate appeared to involve the larynx and a tracheotomy was performed with temporary relief.

The common cold and upper respiratory disease generally (with the exception of otorrhoea) were not much of a problem. Chronic nasopharyngitis in children, so familiar in England, was practically never seen. Sinusitis was rare. The brunt of the widespread respiratory catarrhs fell upon the bronchi and lungs.

Both acute otitis media and otitis externa are common among Ibadan children of all ages. Recurrent otorrhoea with chronic perforation of the drums is one of the more frequent reasons for attendance. The discharge can be suppressed in most cases by a week of procaine penicillin, to obtain which they come to out-patients. There were many cases also of acute laryngitis, and tracheotomy cases were a commonplace. Chronic respiratory illnesses, whether asthma, bronchiectasis or fibrotic lung were scarce.

Protozoal and Helminth Infections. The incidence of malarial parasitaemia in random samples of the population is fairly accurately known in this area; for example Walters (1956) found in Ilobi the following percentage of malarial parasitaemia:

Age (years)	%
0–1	50
2–4	76
5–9	76

P. falciparum was far the commonest, and a mixture of *P. malariae* and *P. falciparum* next. Occasional *P. ovale* infections were seen. The adult parasite rate was approximately 30%. In Ibadan school children, Garlick (1956) found in the age group 5 to 7 years, 84% parasitaemia (77% *falciparum*, 20% *quartan* and 3% *ovale*; the number of mixed infections was considerable). In out-patient work with children, malaria is very common and heavy parasite densities even in infants were frequently discovered. Infection was quickly overcome with treatment. Patients ill from other causes often also developed malaria and one had to be ready to accept a sudden temperature as an indication for anti-malarial treatment in children in and out of hospital.

Though it is clearly desirable, it was not found possible in 1956 routinely to stain blood films of all children with fever on admission to hospital. It follows therefore that a majority of the cases classed here as malaria were clinical, or presumed, and this presumption was based on a rapid subsidence of symptoms after anti-malarial treatment. A common story was fever and convulsions of sudden onset in a young child, who was semi-comatose and collapsed when admitted. Response to chloroquine was dramatic and consolidated the clinical diagnosis. Although an initial convulsion is common with a malarial infection, true cerebral malaria in a child was not proved to my satisfaction in any case.

Amoebic dysentery was not very common among Ibadan children, but, when present, was usually the cause of severe illness. There were in fact seven deaths in 16 cases. There were only two cases of amoebic hepatitis.

Ascaris infestation is almost universal and seems to cause very few symptoms unless the child is unfortunate enough to become obstructed by a mass of worms in the intestine. This happened twice in this series and both children required laparotomy and worm removal. Whether the abdominal pain that is a common complaint in out-patients is ever related to ascaris infection is debatable. There seems little point in eradicating average worm infestations because of the certainty of return within a short time in this environment. Stool examinations were made on only a few in-patients, and neither there nor in routine reports on out-patients were the ova of hookworm (unlike round and whip-worm) frequently mentioned. This infestation does not appear to be a significant factor in the common anaemias of Ibadan children. Guinea worm is common but there is no effective hospital treatment. For this reason perhaps, fresh cases of guinea worm were not often seen, but late effects, such as abscess formation, sterile cystic collections around the track of the worm, cheloid scarring and sometimes radiographic demonstration of calcified guinea worms were noted many times.

Unexplained and Unclassified Illness. The frequency of obscure and fatal illness is one of the most tantalizing aspects of tropical paediatric practice. Fever with repeated convulsions and ensuing coma was a particularly familiar grouping of fatal symptoms. Such cases, if they did not rapidly respond to anti-malarial drugs, had a bad prognosis. Meningitis was excluded in all of them. In a number necropsies were performed without finding a cause for death. The picture was clinically that of acute encephalitis. More than half these cases died.

Infections of Skin, Lymph Glands and Subcutaneous Tissues. Superficial septic infections were a very important cause of morbidity in children. Of this group of 64 hospital in-patients, one third were newborn infants. In these the complications of umbilical sepsis were the main trouble. It can be truly said that trivial umbilical infections were not often seen, but that dangerous infections were not infrequent. Cellulitis spreading from the navel, and sometimes extending into the pelvic tissues, occurred 11 times and tended to be fatal. *E. coli* was the usual pathogen. Another form of cellulitis that was seen in babies affected the scalp, spreading with alarming rapidity to produce islands of necrosis of the whole thickness of the scalp, leaving large raw areas to be repaired.

At all ages, these children are very subject to multiple subcutaneous abscesses. So-called acute pyomyositis, from which a bacterial causative agent can rarely be recovered, was seen only once; it is a condition mainly confined to young adults. There were two cases of a curious low-grade retro-orbital cellulitis which were not satisfactorily explained or treated. A suppurative lymphadenitis of the iliac glands was a disabling and not unusual condition.

Staphylococcus pyogenes was responsible for the great majority of these septic conditions. Among in-patients it was found in 1956 that 60% of the staphylococci in the Adeoyo Hospital were resistant to penicillin, and among out-patients 35%. About a quarter of in-patients and one seventh of out-patients, moreover, were infected with aureomycin-resistant strains of staphylococcus.

In out-patients, skin sepsis of all kinds accounted for as many attendances as any other condition. Furunculosis about the head and shoulders, to which infants seem especially susceptible, impetigo, pemphigus, cellulitis and abscesses of all kinds were commonplace. Fortunately the *in vivo* response to penicillin seemed better than would be expected from the laboratory figures for drug sensitivity, and most skin sepsis could still be controlled quickly by a daily injection of procaine penicillin for three to four days, supplemented where necessary by incision. Among older children, tropical ulcers around the ankles (Fig. 8), with moist red bases and exuberant edges, were very common, and although no specific organism was isolated, the response to penicillin and eusol dressings was favourable and rapid.

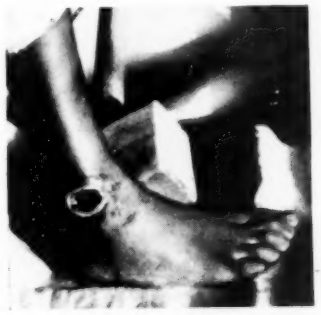


FIG. 8.—Tropical ulceration.

Other Acute Specific Infections. Organisms of the *Salmonella* genus appear to be widespread in the

Ibadan area, and can be recovered from a number of domestic animals and from lizards. We encountered infections at all ages in childhood. Clinical presentations varied from very subacute to the most severe illnesses. There were seven proven cases of infection by *B. typhosus*, and three of these died. *Salmonella* was recovered from certain cases of septicaemia in infancy, at which stage it is one cause of infective jaundice of the newborn.

Possibly the most interesting group were those five cases (all of whom were under 18 months old) who had a salmonella osteitis. Other examples were seen among out-patients. This is a lesion almost confined to young children with sickle cell anaemia. The bones chiefly affected were the small ones of hands and feet; in two the scapula was involved. A feature of this osteitis was its quiet presentation, and the absence of any systemic illness. The disorder appeared to be self-limiting and recovery complete. A typical x-ray picture in which osteolysis predominates can probably be recognized. This association has been reported before in the Belgian Congo, in Jamaica and in the United States, *vide* Golding (1956).

Whooping cough was the only one of the common infectious diseases of English children that proved at all common in Ibadan during 1956. Those admitted nearly all had broncho-pneumonia and ran a long course; they were mainly infants. Several infants severely ill with whooping cough developed an encephalopathy which was usually fatal. Such a child would have convulsions, with steadily diminishing awareness and a progressive rigidity of the limbs. The cerebrospinal fluid was normal. Two points were helpful in out-patient diagnosis of whooping cough. First, a tendency to a more generalized oedema than is usual in English children with a paroxysmal cough. Secondly, a tendency to haemoptysis, presumably due to rupture of pharyngeal veins. This was a common reason for bringing a child to hospital, and was almost diagnostic of whooping cough. Cases of secondary yaws were occasionally seen in out-patients, but positive Wassermann reactions were present in only 0·8% of the age group 5 to 9 years, contrasted with 8% in a group of adult males. No case of clinical syphilis was identified.

Diseases of Nervous System. Bizarre syndromes suggesting acute encephalitis were frequent. One, of sudden onset, occurred in epidemic form (see Wright and Morley, 1958). Children with this syndrome were afebrile, and, though rather somnolent, mentally clear. Wild alternating horizontal movements of the eyes occurred spontaneously, as well as violent agitation of the trunk and limbs on attempting to sit up, or even to raise a leg or arm. There was no disturbance of the C.S.F., and fortunately all the cases recovered in the space of a few days and were left with no immediate sequels.

There were other cases who came in with convulsions and remained unconscious with various pyramidal signs, and in some but not all there was a pleocytosis in the cerebrospinal fluid.

A most interesting group comprised seven children with roughly similar symptoms, in whom there was a sudden onset of hypotonia and weakness of a part of the skeletal musculature. Tendon reflexes were preserved or exaggerated. Flaccidity was so profound that in a bad case the child could not even sit up or hold the head steady. In some there was elevation of cell count or protein level in the cerebrospinal fluid. There were no sensory changes, and these children tended to recover but might relapse. The picture was complicated, however, by the fact that hemiplegia occurred in at least one of them and was permanent, while in others flaccid palsy of one or more limbs persisted. One of these children died of respiratory failure. A number of children were observed who had the permanent residua of illnesses that sounded like encephalitis. Some had convulsions, some mental backwardness, as well as a group with parkinsonism and other basal ganglionic disorders, including oculogyric crises, suggesting a kinship with encephalitis lethargica. The label 'acute poliomyelitis' must be used with caution, but we saw some children who developed flaccid palsies of a number of muscle groups in the limbs during a febrile illness with a mixed pleocytosis in the cerebrospinal fluid, and in some out-patients an isolated flaccid palsy of the limbs of abrupt onset underwent the same sequence of gradual but often incomplete recovery that we are familiar with in poliomyelitis.

It is difficult to say if mental deficiency of primary type is more or less common than in Britain. There are certainly many examples. During the year about 10 mongols were seen. Much mental deficiency is acquired after inflammatory processes in the nervous system, and we diagnosed one defective child on clinical grounds as a case of toxoplasmosis. Two cases of microcephaly were seen. I did not see a cretin during the year. A number of cases of primary cerebral agenesis with palsy were also seen.

Recurrent convulsions in children are not a reason for bringing them to out-patients in Ibadan; in Britain such cases form an important part of clinic work.

Diseases of Genito-Urinary System. Nephrosis is one of the big clinical problems among Ibadan children but it is not encountered much in adults. Such cases present as a Type 2 nephritis, with proteinuria and oedema, without cell deposit in the urine, nor any nitrogen retention. Some of them go on to develop hypertension and azotaemia in a year or more. Some seem to remit quickly and spontaneously, and it was my impression that these remissions were assisted by using penicillin in the first stages. The prognosis for recovery may be better than in British children and several returned as far as can be judged to normal, without residual proteinuria, within a year. A large number continue to run a fluctuating course in out-patients, and their eventual fate remains to be seen. There is nothing in the preceding history of these children that appears to account for the onset of nephrosis. A few start as young as 2 years, but most have been between 3 and 6. Whether the reputed association between quartan malaria and nephritis has any relevance is a matter worth investigating. The infection rate among this group of oedematous children was very low, which contrasts with their susceptibility to pneumococcal infections in Great Britain. Type 1 nephritis, though encountered, was unusual.

Diseases of Bones and Joints. Acute osteomyelitis in young children was very common. A multifocal infection involving simultaneously many bones in several limbs, usually without much systematic upset except some fever, was a frequent and interesting condition. Sometimes there was an associated septic arthritis, or subcutaneous abscesses. The staphylococcus accounted for the majority, but as already mentioned, *Salmonella* was a common pathogen when the child also suffered from sickle cell anaemia. Radiographic changes were early and gross. The mandible was sometimes involved, and the ribs, but predominantly the limb bones. The fairly benign course is reflected in the single death out of 26 cases. Nevertheless, it was often weeks before pus ceased to form at the site of bony swelling, and several patients ran through a wide range of antibiotics before recovery. With the exception of occasional sequestrectomy, surgical measures were seldom necessary; even where sinuses formed, eventual healing occurred. Amyloid disease was not seen in any child during the year.

Acute septic arthritis affected children under 3 years of age. Very often it was an extension of a neighbouring osteomyelitis, but sometimes the joint involvement was primary and the process was then frequently multiple. Surprisingly, intense pain was rarely present and again we were struck by the comparative absence of constitutional illness. These children did well after aspiration of pus from the joints and appropriate chemotherapy; most of them too were infected with the staphylococcus.

Purulent Meningitis. There were 36 cases of acute meningitis and a causative organism was not identified in 15 of them. Preliminary out-patient treatment with penicillin or a sulphonamide may have been sometimes given, but even so the failure rate seems surprisingly high. Of those we did identify, eight were due to *Haemophilus* (seven of these under 1 year old), and another eight to *Pneumococcus* (six of whom were infants). Two infants died of *E. coli* meningitis. In the whole series there was only one meningococcal infection, but possibly this organism was one of those that failed to grow in culture. However, it is well-known that meningococcal meningitis is a scourge in the drier northern parts of Nigeria, and is much less prevalent in the South. With 13 deaths, we cannot be very proud of our results. Many of the cases were advanced when we got them. There was one case of *Ps. pyocyanea* meningitis, and one due to *Haemophilus bronchisepticus*.

Tumours. This group differed little from what might be encountered in a British children's hospital. The strawberry naevus, so common in British babies, was not seen during the year. There were examples of nasopharyngeal lymphosarcoma and bilateral ovarian carcinomata, both of which seem to be of relatively high incidence around Ibadan.

Other Nutritional and Deficiency Diseases. A large number of our patients were chronically underfed. It was only where the resulting emaciation was of such a degree as to require urgent admission to hospital that they appear in this analysis. There were 18 such cases. Very often the mother was herself in poor condition and attempting to feed twins. If she believes that her breast milk is insufficient a very watery maize pap is provided as a supplement, and on this it would be difficult to gain weight. As important as deficiency in food is deficiency of water, and many of these malnourished babies were dehydrated; another reason for their admission. Some marasmic infants, with no other cause than underfeeding, would weigh no more than 7 or 8 lb. at a year old. Vomiting from underfeeding does not seem to happen as in Britain. In fact, vomiting in babies, whether with gastro-enteritis, feeding

difficulties or parenteral infections, was strikingly infrequent.

Of the vitamin deficiencies, only two were recognized. These were rickets and riboflavin deficiency. The latter was seen as soreness of the tongue with angular stomatitis. Rickets is not very uncommon in Ibadan children, as Jelliffe (1955) has previously pointed out. Most cases were picked up in infants of about 3 months old. A number of these had been premature, and others shielded from the light as for example by their mothers being in purdah. The main pathogenesis, in fact, was prematurity with overclothing. Some florid examples were seen, but easily corrected with calcium and vitamin D.

Cardiac and Circulatory Disease. No case of acute rheumatism was recognized in 1956. Congenital heart disorders were probably encountered less frequently than in a comparable child population in the United Kingdom. For example, no severely handicapped heart case was seen among the 6,000 hospital births in the year. There were seven cases of what we have termed 'cardiomegaly with heart failure'. Broadly speaking, there are two varieties of this obscure malady, which is common among both children and adults in the locality. The first group consists of rather quiet hearts that are generally enlarged and that present first with congestive failure. There are few or no murmurs and the failure can be compensated after rest in bed and the use of digitalis, but the life of the child is subsequently very precarious and his exercise tolerance severely restricted. Follow-up is not long enough to establish how long these children live after this sequence has taken place. In the other group the hearts are also large, but there is a severe lesion of the mitral valve which is always incompetent and sometimes stenosed. Invariably there are signs of pulmonary hypertension. Some of these too, have been in failure, but others have come to light only when the children were examined for other disorders. That this is an acquired disorder is virtually certain. Nearly all are upwards of 3 years old. There was nothing suggestive of acute rheumatism in these children, who were afebrile, not anaemic, not ill, and younger at onset than is the case with European acute rheumatism. One died in what appeared to be an exacerbation of a chronic cardiopathy, and at necropsy some pericarditis was found, besides endomyocardial fibrosis with thickening and distortion of the mitral valve and the adjacent endocardium. Both the clinical and post-mortem appearances are precisely those of endomyocardial fibrosis as first described by Bedford and Konstam (1946) and in more detail by Williams, Ball and Davies (1954) in East Africa. This is the commonest form of heart disease of young people in tropical Africa. Its aetiology is still quite obscure. Certain other cases of this disorder were seen and followed in out-patients. There is little that one can do to help, though it is of course important to map the natural history of this disease in childhood, but we did get the impression that digitalis was useful for some of the patients who were on the brink of congestive failure.

Neonatal Diseases. Seven infants, all aged less than a week, were admitted with a very deep jaundice and two of these died. The local causes of neonatal jaundice have not been elucidated. Some babies, I think, were merely suffering from physiological jaundice aggravated by an inadequate fluid intake. Others may have been cases of infectious jaundice such as are recorded elsewhere in this analysis. Although we made some attempt to exclude haemolytic disease of the newborn by Coomb's tests and never discovered it, one cannot be sure that there were not examples of this disease among our infants. The very high level of rhesus-positive blood groups among this population makes the chance of rhesus incompatibility between mother and child much lower than in Britain.

Immaturity at birth is a great addition to the many physical dangers attending the growth of an African child. Premature birth is nevertheless a very frequent event in Africa. During the year under review 169 infants (not included in the table of admissions) were reared in a premature nursery attached to the Maternity Department. All of these weighed under 2,000 g. (4½ lb.) at birth, and comprised about one half of all infants born in hospital in this weight category. (Of the 6,000 annual births in hospital some 850 were under 5 lb. birth weight.) Two thirds of these premature births were twin births (the incidence of twinning is 4·2% of all births). It may be said that in the early weeks by using the simplest methods it is possible to obtain in Africa survival rates nearly as gratifying, weight for weight, as in Europe or America. The figures are improved because the gestation period of an African baby of given birth weight has usually been longer than that of the European. Most were spontaneous premature deliveries. There was a lessened risk of death within the first 48 hours of life by comparison with European figures, possibly accounted for by the infrequency of lethal congenital malformation, of haemolytic disease of the newborn, of the alveolar membrane syndrome and of severe chilling after

birth. In spite of a congested nursery and a rapid turnover, sepsis occurred in only 14% of babies; it was mainly as in Britain of skin and eyes. In spite of the tropical climate the temperature of small babies tended to fall, and sclerema neonatorum was several times encountered; chilling was a more frequent event than overheating. We are unfortunately almost totally ignorant of the later career of these babies after leaving hospital.

Diseases of Liver. Cirrhosis of the liver, though an important entity in adult practice in Ibadan, was unusual in children, and there are only four examples in the series. If protein malnutrition had this sequel we would be certain to see more cases in older children.

Diseases of Eyes. Corneal ulceration is not a condition that finds its way into hospital very much, which accounts for the fact that we only list four cases here. Corneal ulcers, however, are a big factor in the morbidity of children in this area, and they happen not infrequently during infectious illnesses, especially if the child's nutrition is reduced. It is distressing to see how many children in the streets have corneal nebulae, and of course in the northern provinces of Nigeria trachoma adds to the high incidence of blindness in West African young people. Phlyctenular conjunctivitis may go on to ulceration, and corneal opacities also derive from this. The sequel to corneal ulcer is only too often perforation and shrinkage of the eye and blindness.

Poisoning and Idiosycrasy to Drugs. Very few cases of poisoning came into hospital. Kerosene came first as an agent with three victims, and then accidentally-swallowed caustic alkali. There was another group who were said to be suffering from 'native medicine poisoning'. Undoubtedly a large number of our children, especially those who had had convulsions, smelt strongly of an ammoniacal mixture containing urine, which is used in Ibadan as a medicine. Just how important this is in producing symptoms I am not sure. Some of these children, certainly, remained limp and unconscious and died. Others, however, smelling no less strongly and appearing no less ill, recovered and it is my feeling that the native medicine really plays a rather insignificant role. Further south, nicotine and other alkaloids are employed in native medicines, and potent agents may sometimes be given to children here, but the onus of proof that these neurological symptoms are a result of attempted treatment rather than of the disease itself still rests with the exponents of this idea.

Final Remarks

Certain conditions commonly met with in European practice were encountered too seldom to figure as important. Examples are streptococcal infections and their complications, asthma and kindred psychosomatic disorders, the collagen disorders and some others already referred to. Certain congenital defects were less common than in England, and no case of congenital pyloric stenosis was seen during the year. Nevertheless, the above account demonstrates that we were not confronted in Nigeria with a continuous parade of children suffering from tropical disease in the generally understood sense, nor was the common paediatric currency of England by any means superseded. Though it was true that more than one pathological condition was often present in our young patients it was seldom difficult to disentangle them, or to determine which was dominant in a given clinical situation. In this respect tropical practice among children is less confusing perhaps than among adults, in whom long-standing processes tend to blur the clinical outline of disease.

When the range of normal in all the territories of clinical and laboratory medicine is as yet unmapped and prevailing methods of treatment for many disorders are so discouraging, a great need exists for the collection of data and for clinical research. The teaching of medical students demands an imaginative adaptation of European techniques to fit the widely different local situation. Besides all this, there is the insistent tumultuous pressure of patients, who by their very numbers have power to submerge the medical staff beneath a horizonless sea of routine. Here is opportunity indeed for those with vision and talent, and many will be needed if standards of paediatrics throughout tropical Africa are to be enabled quickly to rise.

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PHLYCTENULAR CONJUNCTIVITIS IN AFRICAN CHILDREN

BY

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Phlyctenular conjunctivitis is a focal inflammatory disease of the conjunctiva characterized by a rounded translucent nodule surrounded by a zone of hyperaemia. The nodule may be single or multiple and is situated on the conjunctiva, close to the corneal limbus. Histologically it is an aggregation of large numbers of lymphocytes and occasional polymorphonuclear cells. Secondary infection, photophobia, blepharospasm and lacrimation are features of this condition.

Phlyctenular conjunctivitis is relatively rare among Europeans, but is still common in non-European communities. In 1947 an American Medical Association investigation committee (Barnett, Fields, Milles, Silverstein and Bernstein, 1947) reported that 20% to 50% of children in Alaskan native villages had corneal scars, due to healed phlyctenulosis. Thygeson (1951) noticed a very high incidence of this condition among Apache Indians of Arizona during the years 1934 to 1938 and among the Negro and Puerto Rican children of New York City before World War II.

At Baragwanath Hospital where we deal with an African urban community living under poor hygienic circumstances we see active phlyctenulosis among the children quite commonly. At the Children's Outpatient Department which is attended by children up to 9 years of age, and where the total yearly attendance of new cases is 40,000, 36 active cases of this condition were seen in a 12-month period. We were particularly interested in elucidating the relationship of these cases to tuberculosis which is rife in the community.

The Present Study

This study was done retrospectively and is based on the records of all cases of active phlyctenular conjunctivitis seen at the Children's Outpatient Department in the 12 months from November, 1955, to October, 1956. There were 36 in all.

The age range among our 36 cases was 1 to 9 years, the majority of them being 4 to 8 years old. A slight preponderance of females, 19, to males, 17, was noted, and there appeared to be no month or season in which the cases presented predominantly. The standard of nutrition was average for urban African children in Johannesburg, except for one child who was so malnourished that he was specifically admitted for this.

All of the 36 cases had radiographs of the chest taken. Unfortunately, due to a fear of the excessively strong allergic reactions to tuberculin which have occurred from time to time in this condition, only 17 of the 36 were tested for tuberculin sensitivity, using the tuberculin jelly patch test. Of these 17 cases 15 showed positive reactions, three of which were severe with blistering and tissue necrosis, and two were negative. The radiological survey showed 22 cases with definite evidence of active or healed tuberculosis and of these, five cases had calcified tuberculous lesions (Fig. 1a and b). Fourteen cases had completely normal chest radiographs. One case had associated erythema nodosum and another case had a tuberculide rash.

Discussion

Price (1948) states that the majority of cases of phlyctenular conjunctivitis occur within the first 5 years of life. In Sorsby's (1942) series the age of maximum liability was from 4 to 10 years. Thygeson's cases occurred most commonly between the ages of 8 to 15 years. Our cases occurred predominantly between 4 and 8 years.

Both Sorsby and Thygeson state that the condition is more common in females. In our cases there was only a slight predominance of females over males. Sorsby noted that this condition presented more commonly in Spring; in our cases there appeared to be no seasonal variation.

Malnutrition, focal sepsis, pediculosis and worm infestation have all been incriminated as aetiological agents from time to time. The findings in this

series do not support these views. Thygeson states that phlyctenulosis is most frequent in children from the lower economic strata of society whose diet is most likely to be deficient. Our cases all occurred in a predominantly malnourished society, but only one was severely malnourished, the nutrition of the others varying within the average range.

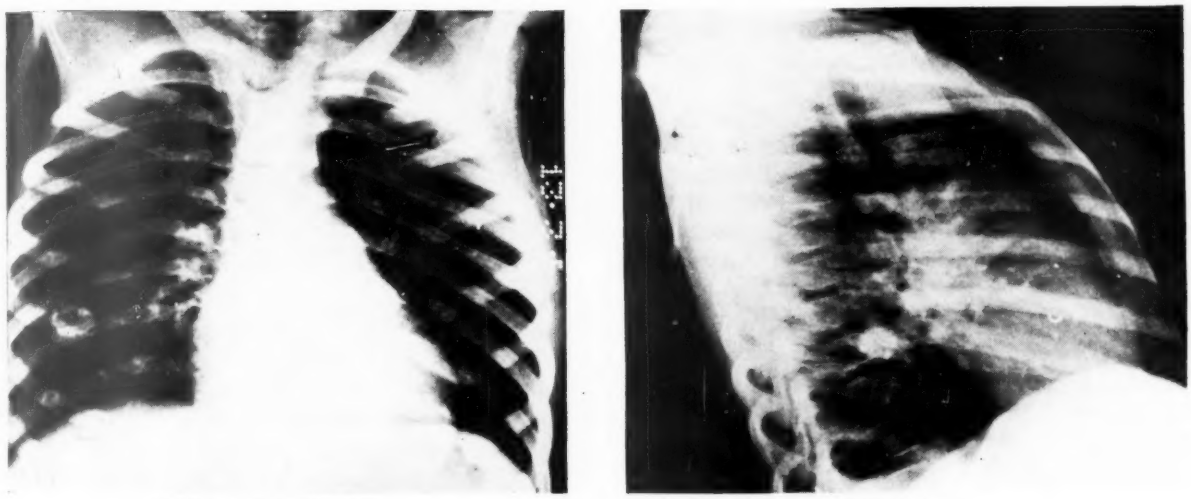
Most writers stress the aetiological importance of tuberculosis, although there is considerable disagreement about the specific phase of tuberculosis with which it is associated.

Sheldon (1955) states that phlyctenular conjunctivitis and erythema nodosum are benign allergic manifestations of primary tubercle occurring at the time of Mantoux conversion and that their presence indicates early tuberculosis. Holt and McIntosh (1940) state that phlyctenular conjunctivitis may occur at the height of the initial tuberculous infection but that it is more common later and shows a tendency to recurrence and chronicity; they also state that it is invariably a manifestation of tuberculosis and is accompanied by a high degree of allergy. Lightwood and Court (1953) claim that, although there is clearly a relationship between tuberculosis and phlyctenular conjunctivitis, the oft-repeated statement that phlyctenulosis is strictly analogous to erythema nodosum is not true and its onset bears no fixed relationship to the emergence of primary tuberculous allergy; they feel that it is best considered as a response to sensitization by several allergens of which in Great Britain tuberculosis is the most important. Ellis (1956) states that as in the case of erythema nodosum, phlyctenular conjunctivitis is regarded as an allergic manifestation for which tuberculous infection elsewhere in the body is responsible in more than 75% of cases. Whilst non-tuberculous cases may occur and while there appears to be some relationship with malnutrition, it should always be assumed that tuberculosis is an aetiological factor until investigation has proved otherwise.

When Fritz and Thygeson (1951) investigated phlyctenular conjunctivitis in Alaskan Indians and Eskimos they found that all cases of active phlyctenulosis had positive tuberculin reactions, while radiographic evidence of active or inactive pulmonary tuberculosis in a comparative study of two Alaskan villages showed a parallel between the prevalence of tuberculosis and phlyctenular conjunctivitis.

Sorsby (1942) writing on phlyctenular conjunctivitis in children and adolescents in England, found that in 592 cases 84·8% were tuberculin positive, as against 15·3% in 900 control cases, and that of 510 cases examined radiologically 72·2% showed evidence of pulmonary tubercle as against 16·1% positive radiographs in 87 controls. The same author investigating the family history of tuberculosis found an incidence of 28·9% in 263 school children with phlyctenular conjunctivitis as opposed to an incidence in the normal school population of 3·7%. The expectation of subsequent overt tuberculosis was statistically higher in the phlyctenular conjunctivitis group.

Damato (1951) reports the cases of 11 children in



(*a*) *Posterior-anterior view.* (*b*) *Lateral view.*

FIG. 1 (*a*) and (*b*).—Chest radiographs showing calcified primary focus in lungs of patient with phlyctenular conjunctivitis.

Malta who developed phlyctenular conjunctivitis two to six weeks after BCG vaccination and he concludes that this is evidence that phlyctenular conjunctivitis is due to sensitization with tuberculoprotein. He also attributes the lowered general incidence of phlyctenulosis in Malta in recent years to the lowered incidence of tuberculosis brought about by BCG innoculation.

Fritz and Thygeson (1951) consider that phlyctenular conjunctivitis in well-developed tuberculosis may be due either to activation of an already existing focus of tuberculosis which liberates antigenic products into the blood stream or to nonspecific vasodilatation caused by secondary bacterial infections of the eye bringing circulating tuberculous antigens to the conjunctivae. They have repeatedly observed the effect of epidemic Koch-Weeks bacillus and pneumococcal conjunctivitis in exciting acute attacks of phlyctenular conjunctivitis in susceptible children.

Our series of cases appears to confirm the view that phlyctenular conjunctivitis is commonly associated with tuberculosis. An interesting finding was that of associated long-standing tuberculous infection as evidenced by calcified lung lesions in five patients. As far as we could determine all the patients were suffering from phlyctenular conjunctivitis for the first time since there was no evidence of old scarring. This suggests that although there is a link between phlyctenular conjunctivitis and tuberculosis, the condition is not necessarily associated with the early hyper-allergic phase of tuberculosis occurring at the time of Mantoux conversion, i.e. approximately six weeks after the initial infection. We feel that this supports the view that phlyctenulosis is not analogous to erythema nodosum and that its appearance bears no fixed relationship to the onset of primary tuberculous allergy.

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HORMONE EXCRETION IN PRECOCIOUS PUBERTY IN GIRLS

BY

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At puberty in girls the sex hormones are secreted in increasing quantities and the clinical signs of puberty follow. In precocious puberty it is generally accepted that the excretion of these hormones will reach adolescent or adult levels but will not be abnormally high as it may be in tumour or hyperplasia of the gonad or the adrenal cortex. Published reports vary depending on the laboratory investigations carried out, and also from case to case (Fischer, 1940; Novak, 1944; Hain, 1947; Seckel, Scott and Benditt, 1949; Lloyd, Lobotsky and Morley, 1950; Lowrey and Brown, 1951; Mossberg, 1951; Paschkis, 1952; Lloyd, 1955). In general, the 17-ketosteroids tend to be a little higher than normal for the chronological age but they rarely reach more than the lower limits of adult levels and may be quite normal. Gonadotrophin determinations are usually positive, but were negative in the cases described by Gross (1940) and by Bronstein, Luhan and Mavrelis (1942). Oestrogen excretion has been measured by biological methods. The results are difficult to evaluate but on the whole oestrogen excretion tends to be low.

The chemical method recently developed by Brown (1955*a*) has made possible the separate estimation of oestrone, oestradiol-17β and oestriol in human urine. This study was therefore undertaken to assess the clinical value of simultaneous estimations of urinary oestrogens, 17-ketosteroids and gonadotrophins in 11 cases of early or precocious puberty. Vaginal smears were also examined. Hormone estimations were carried out on a control series of 15 normal girls in the age range 3 to 10 years.

Methods

Oestrogens. Brown's method (1955*a*) was used to determine the amount of oestrone, oestradiol-17β and oestriol in urine. The accuracy, precision, sensitivity and specificity of this method have been described (Brown, Bulbrook and Greenwood, 1957). The lower limit for the method has been approximated to be 1·0 μg./24 hours for oestrone and oestradiol and 1·5 μg/24 hours for oestriol. Amounts below this have been recorded as zero. It must be emphasized that oestrogen may be present in such urines but in amounts below the calculated limit of sensitivity for the chemical method. For example, in urine from a normal 6-year-old girl the chemical method gave a value for oestrone below the limit of sensitivity and therefore recorded as zero. However, there was good agreement between parallel chemical and biological assays on this urine using the experimental design of Bulbrook, Greenwood and Williams (1957).

Urinary Gonadotrophins. The method of Dekanski (1949) was used to estimate gonadotrophins. The hormone was eluted from kaolin by 20 ml. of N/10 sodium hydroxide in the initial estimations but subsequently elution was carried out at *p*H 11·0 to 11·2 (Loraine and Brown, 1956). The biological test was done on female mice, 21 days old and weighing 10 g. A positive response was an increase in uterine weight of 100% above controls. Three mice were injected at each dose level and doses were adjusted so that a positive response indicated the presence of 5 mouse units or more.

17-ketosteroids. A method similar to that of Holtorff and Koch (1940) was employed to estimate 17-ketosteroids in urine. This method uses aqueous potassium hydroxide and a control reading, and gives higher results than methods using alcoholic potassium hydroxide and the Talbot, Berman and MacLachlan correction (1942).

Vaginal Smears. Vaginal smears were fixed in ether/alcohol and stained with Harris's haematoxylin and Shorr's trichrome stain. They were graded into negative or positive according to the presence of leucocytes and of keratinization of the epithelial cells.

Case Material

Four cases under the age of 3 years are described, none of whom had regular menstrual cycles. A further seven cases, ranging in age from 6 to nearly 11 years, were children who had signs of early puberty but who could not be classified as being definitely outside the normal range for the onset of puberty (Tanner, 1955). Of 39 children attending The Hospital for Sick Children in recent years because of precocious puberty, 29 fell into the latter group. None of the 10 cases in the former group had regular menstrual cycles.

Where possible, urine for oestrogen determination was collected from normal children in the same age groups as the patients described above.

Results

In 15 normal girls in the age range 3 to 10 years no oestrogen was detected in the urine, with one exception, a 7-year-old girl who excreted 2·9 μg./24 hours. In children over the age of 11 years who had breast development and pubic hair, but who had not menstruated, measurable amounts of oestrogen were found (2·9 to 7·1 μg./24 hours).

Oestrogen excretion, 17-ketosteroid excretion, gonadotrophin excretion and the grading of the vaginal smears of the children with early puberty are shown in Table 1.

In contrast to the control group, nine of the cases in this series were excreting amounts of oestrogen above 1·0 μg./24 hours. In seven of the cases, positive vaginal smears were correlated with the finding of oestrogen in the urine, and in three cases negative smears were correlated with the absence of oestrogen. In Case 1 a negative smear was obtained in conjunction with 1·8 μg. of urinary oestriol, while in Case 5 a positive vaginal smear was obtained but no oestrogen was detected in the urine.

Although the number of cases is too small for statistical analysis there appears to be a good association between the vaginal cytology and oestrogen output, although the latter is very low (2·0 to 6·8 μg. total oestrogen/24 hours). Similar results obtained on a large series of women (Young, Bulbrook and Greenwood, 1957) suggest that a very small output of urinary oestrogen, relative to the amounts in menstruating women, cannot be regarded as too low to be of physiological significance.

Case Histories

Case 1. Aged 7 months when first seen, this baby had a blood-stained vaginal discharge at 4 months. This lasted for five days and was followed by episodes three weeks

TABLE 1

OESTROGEN, 17-KETOSTEROID, GONADOTROPHIN EXCRETION AND VAGINAL SMEAR FINDINGS IN GIRLS WITH PRECOCIOUS OR EARLY PUBERTY

Case No.	Age (years)	Oestrone	Oestradiol	Oestriol	Total (μg./24 hr.)	Vaginal Smear	17-ketosteroids (mg./24 hr.)	Gonadotrophins (m.u./24 hr.)
1	7/12	0·0 0·0	0·0 0·0	0·0 1·8	0·0 1·8	Negative Negative	0·7 (0·47±0·16)	Negative Negative
2	1 10/12	0·0 1·3	0·0 0·0	2·2 4·2	2·2 5·5	Positive Positive	2·5 (1·38±0·66)	Negative Negative
3	2	1·8	0·0	3·4	5·2	Positive	1·6	—
4	2 6/12	0·0	0·0	0·0	0·0	Negative	0·9	Negative
5	6	0·0	0·0	0·0	0·0	Positive	2·1 (2·3±0·85)	Negative
6	8 6/12	0·0 1·2	0·0 0·0	0·0 0·0	0·0 1·2	Negative Negative	4·2	Negative
7	10	3·8	0·0	3·0	6·8	Positive	3·7	Positive
8	8	1·9 2·0 1·3	2·1 0·0 0·0	1·7 2·1 4·2	5·7 4·1 5·5	Positive	4·4	Negative Negative Negative
9	10	0·0 1·4 0·0 0·0 0·0	0·0 1·0 0·0 0·0 0·0	0·0 2·2 1·9 2·5 2·1	0·0 4·6 1·9 2·5 2·1	Positive	4·1	Positive 5–20 5–20
10	10	See Fig. 1			11–38	Positive	5·1	Negative 5–20 10–20
11	10 10/12	See Fig. 1			2·6–29	Positive	7·1	10–20

(The figures in brackets give the normal 17-ketosteroid excretion in children of the age groups: 0–1; 1–5; 5–10).

later and again after a further four weeks. Immediately after admission a profuse menstruation lasting eight days began. Development of the breasts and external genitalia beyond the normal was very slight. The nipples were slightly pigmented. There was a single small patch of pigmentation on the abdomen. Subsequently the periods were very irregular with intervals of several weeks or several months; at the present time no loss has been seen for a year. The vaginal smear and a specimen of urine for oestrogen estimation were taken on the second day after the end of the period which occurred in hospital. The vaginal smear was negative and no oestrogen was detected in the urine.

It was not possible to keep the child in hospital but six months later she was re-admitted for 48 hours for urine collection. The vaginal smear was still negative but 1·8 μg. of oestriol were found in the urine. The 17-ketosteroid excretion was at the upper limit of the normal range.

Case 2. This child was admitted to hospital during the first menstrual loss, which persisted for five days, at the age of 1 year and 10 months. On examination, the breasts were moderately developed and a few pubic hairs were present. The height, weight and bone age were advanced by about a year. Subsequent periods occurred after intervals of two, four, and one month, and lasted from one to three days. A second admission was arranged before the next expected period and specimens taken. The vaginal smear was positive and oestrogen was detected in the urine on both occasions. The gonadotrophin estimation was negative.

Case 3. The child was admitted to hospital at the age of 2 years because of vaginal bleeding lasting for one month. The examinations were carried out during the first one or two days following the cessation of the loss. There was no advance in growth, bone age, or breast development, and no pubic hair. It was thought that she was probably not a case of precocious puberty. Examination under anaesthesia revealed no abnormality which could account for the bleeding, however, and the vaginal smear was positive and oestrogen was present in the urine. The 17-ketosteroids were normal. No specimen was obtained for gonadotrophin estimation.

Case 4. This child was admitted to hospital because of congenital dislocation of the hip. At the age of 2½ years she was observed to have pubic hair and minimal breast development. Her growth and bone age was not advanced. The vaginal smear was negative, no oestrogen or gonadotrophin could be detected in the urine. The 17-ketosteroids were normal. This case demonstrates that clinical signs of precocity may be present in the absence of any confirmatory laboratory tests.

Case 5. At the age of 6 years this child had the weight, height and bone age of a child of 8, 10 and 11 years respectively. The breasts were very well-developed. There was no pigmentation of the nipples, no pubic or axillary hair, and the vulva was not developed. On rectal examination, the cervix and uterus were not palpable. There had been no menstrual loss. The vaginal smear was positive in this case although no oestrogen could be detected in the urine.

Case 6. On examination at the age of 8½ years, some breast development had taken place; there was much pubic hair and some axillary hair. No menstruation had occurred. The 17-ketosteroid excretion was just above the upper limit of normal (mean $+2\times$S.D.). Oestrogen was detected in one of two specimens of urine examined.

Case 7. On examination at the age of 10, the height, weight and bone age were in advance of the average by about two years. The breasts were developed and pubic hair was present but menstruation had not occurred. The first period, lasting one day, began five weeks after this examination. Hormone excretion was indicative of puberty; oestrogen and gonadotrophin were present in the urine and the vaginal smears were positive.

Case 8. This child was seen at the age of 8½ years. A few pubic hairs and slight development of the breasts had been noticed for about six months and on one occasion there had been a slight loss of blood for one day. Her height, weight and bone age were all advanced by three or four years. During the next two years she had slight shows of blood, never lasting for more than one day and occurring at intervals of one to three months. Oestrogen was present in three specimens of urine; the vaginal smear was positive and the 17-ketosteroid excretion was just above the normal range for the age. Though gonadotrophin was persistently absent from the urine, it was eventually demonstrated to be present when the patient reached the age of 10 years and regular periods had commenced.

Case 9. When first seen, at the age of 10 years, there had been irregular menstrual loss for a year. The breasts were developed and there was scanty pubic hair. The height was advanced by two years but not the bone age; she was very obese. Weekly specimens of urine were obtained in an attempt to demonstrate cyclical ovarian activity, but the number of specimens available were too few for this. Of five urine specimens, four contained oestrogen. Gonadotrophin was present in the urine.

Case 10. First seen two weeks after the first period, at the age of 10 years; her breasts were developed and pubic hair was present. The height and weight were advanced about four years. Periods have continued at fairly regular monthly intervals. Urine specimens were collected at intervals throughout the cycle and the details of oestrogen excretion are shown in Fig. 1.

Case 11. Breast development was first noticed at the age of 8½ years. Menstruation commenced at 10½ years and continued at regular monthly intervals. When seen at the age of 10 years and 10 months, the height, age, and bone age were those of a girl of 15 years. The cycle of oestrogen excretion is illustrated in Fig. 1.

Certain miscellaneous findings are of interest. In a case of polyostotic fibrous dysplasia, aged 7 years, with early signs of precocious puberty but no menstrual loss,

oestriol excretion was 1·6 μg./24 hours; the 17-ketosteroids 1·4 mg., and the gonadotrophins negative. The vaginal smear was negative. In a boy, aged 8, with gynaecomastia of one breast, the oestrogen excretion totalled 4·5 μg./24 hours on one occasion and zero on two others. In one case of idiopathic breast development the vaginal smear was negative, no oestrogen could be detected in the urine, and the 17-ketosteroids were 0·6 mg./24 hours at the age of 15 months; the bone age was advanced six months. Material from a second patient in another hospital was also examined. The vaginal smear was positive; the total oestrogen excretion was 2·7 μg./24 hours, and the 17-ketosteroids were 1·2 mg./24 hours at the age of 3½ years. Gonadotrophin was less than 5 m.u./24 hours. There was apparently no clinical evidence of precocity. Upon enquiry it was learned that breast development regressed after 12 months. The presence of oestrogen in this case suggests that a true precocity was present. In a case of Klinefelter's syndrome in a boy aged 15 with gynaecomastia, gonadotrophin more than 72 m.u. and female genetic sex, the total oestrogens were 4·8 μg./24 hours.

Three normal boys and a girl, in hospital for tonsillectomy, had urines collected on the day of the operation, on the day before and the day following. Although the 17-ketogenetic steroids rose four-fold on the post-operative day, the level of oestrogen excretion was less than 1·0 μg. in all four cases on each of the three days. This result contrasts with similar studies in adult men in whom a rise in oestrogens accompanies the rise of other adrenal steroids following surgical stress.

Discussion

Biological assay results for urinary oestrogen excretion in normal children show considerable variation. For example, Nathanson, Towne and Aub (1941) found levels of up to 5 I.U. of total oestrogen in children of both sexes up to the age of 7 to 8 years, rising to 20 I.U. at the age of 11, and 240 to 382 I.U. in girls between the ages of 13 to 15 years. Dorfman, Greulich and Solomon (1937) found levels of 0 to 25 I.U. in five girls of ages varying from 7 to 12 years, while Pedersen-Bjergaard and Tønnesen (1948) found levels of up to 3 m.u. between the ages of 3 to 12 years. In one of the five cases of precocious puberty described by Hain (1947), the urinary oestrogens were 200 I.U./24 hours, and in the case reported by Gross (1940) they fluctuated between 405 and 12 I.U.; but this is exceptional and in the majority of reported cases oestrogens were absent or less than 10 I.U./24 hours. In his series of nine cases, Novak (1944) reported laboratory results as essentially negative in five; oestrogen levels were 4·4, 4·0,

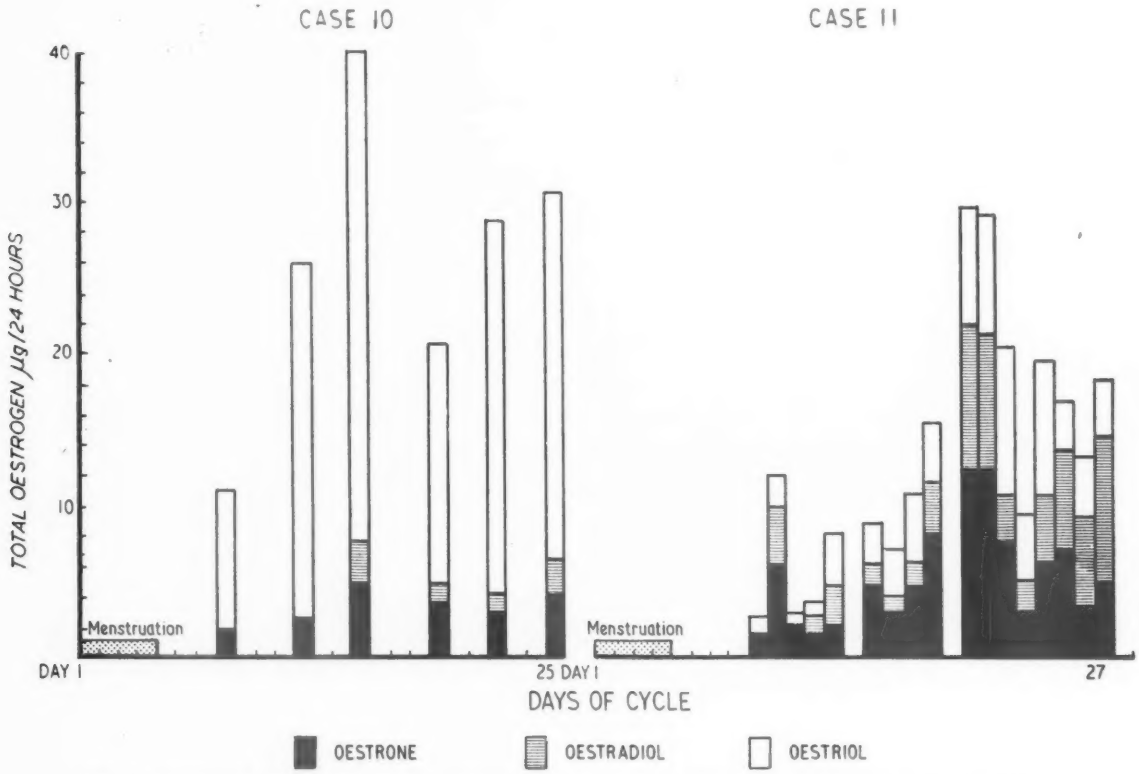

FIG. 1.—Oestrogen excretion during the menstrual cycle. Case 10, aged 10 years; Case 11, aged 10 years 10 months.

and 25·0 I.U. in three, and slightly lower than the normal pubertal level in one.

Although this study is concerned with only a small number of cases of precocious puberty, certain conclusions may be drawn. First, children who have developed certain of the secondary sexual characteristics, advanced growth, breast development and pubic hair, but who have not established regular menstrual cycles, excrete much less oestrogen than adult women (Brown, 1955*b*). It is not known whether the oestrogen excreted by children with precocious puberty is of adrenal and/or ovarian origin. Secondly, oestrogen excretion is nevertheless almost certainly greater in this group than in normal children without any of the signs of approaching puberty. Thirdly, a dramatic rise in oestrogen excretion occurs with the appearance of regular menstrual cycles undoubtedly of ovarian origin. This is illustrated by the two girls, both under 11 years of age, who had regular cycles and who achieved adult levels of excretion. It is probable that there is no essential difference between normal and precocious girls in these respects. It is not possible to say whether an *infant* with regular cycles would show this dramatic rise in excretion since none of the cases described here had the fully developed syndrome. This type of case appears to be uncommon since in Jolly's series of 31 cases only six had had regular cycles before the age of 8 years (Jolly, 1955).

Nathanson *et al.* (1941) reported that about a year and a half before the menarche, oestrogen excretion becomes cyclic in girls, and the intensity of these cycles gradually increases; it is possible that there is a rise and fall in oestrogen and in gonadotrophin excretion in precocious puberty. If this is so, estimations on single 24-hour specimens are necessarily of limited clinical value. Higher values may have existed in our cases and been missed, notably in the three infants who presented with bleeding.

Gonadotrophin was present in the urine of Cases 7, 9, 10 and 11, but absent in Cases 1, 2, 3, 4, 5, 6 and 8. In their extensive study of gonadotrophin excretion by the pre-menarche child, Catchpole and Greulich (1943) estimated the hormone in 24-hour urines every day for at least a month in 16 normal girls. With the approach of the menarche the number of days in which they were able to detect FSH in the urine approximated to 100% while the level of excretion also rose. The results in each case varied with the proximity of the first period. The average time elapsing between the date of the estimations and the date of the menarche in their cases was seven months, while the average percentage of days on which hormones could be detected at a level of 2 m.u. or more was only 43%. In adult women, Levin (1941) found that the daily excretion of gonadotrophin was less than 7·5 m.u. per day during the greater part of the cycle, but peak periods lasting for two days occurred at the mid-cycle when excretion rose to 15 m.u./24 hours in one case and 35 m.u./24 hours in another. It seems probable, therefore, that the absence of gonadotrophin from the urine of some of these cases may be due either to the insensitivity of the test, or to the irregular excretion of the hormone.

Vulval bleeding from local causes may mimic menstrual bleeding if the cause is not obvious on examination. In this event the hormone determinations will be normal but this is insufficient ground for excluding a diagnosis of precocity. If, however, the vaginal smear remains persistently negative, even though further bleeding occurs, it is probable that oestrogen excretion is not raised.

It may be concluded from these results that oestrogen, 17-ketosteroid and gonadotrophin determinations carried out on single 24-hour specimens are not diagnostic of precocious puberty, since completely normal values are not incompatible with the diagnosis. Nevertheless, the results demonstrate quite clearly that oestrogen excretion is usually raised above control levels, associated with a positive vaginal smear. With the present chemical method the error of the determinations at the low oestrogen levels encountered in urine from cases of precocious puberty is very large (Brown, Bulbrook and Greenwood, 1957). It may well be that a more sensitive method which could differentiate with certainty between control levels and the small amounts of oestrogen generally found in precocious puberty might be of diagnostic use. Even with the present method of Brown (1955*a*) the results are useful, especially in conjunction with the 17-ketosteroid values, for, if a gross pathological condition in the gonads or adrenal cortices exists, the figures will probably be high, i.e. well within the adult range (Snaith, 1958). This is unlikely to be the case in precocious puberty, except when the periods are well established and not infrequent.

Summary

Urinary oestrogen, 17-ketosteroid and gonadotrophin determinations have been carried out and vaginal smears examined in 11 girls with precocious or early puberty. While the 17-ketosteroid levels are at the upper range of normal values and the oestrogen levels are above control levels, the results of these estimations are not diagnostic of the condition but are of value in differentiating true precocious puberty from precocity due to pathological conditions involving the gonad or the adrenal, and from

non-hormonal vulval bleeding. The results from a control series of 15 normal girls, in the age range 3 to 10 years, are also summarized.

We wish to thank the physicians and surgeons of The Hospital for Sick Children, Great Ormond Street, for permission to study their cases.

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URINARY EXCRETION OF 17-KETOSTEROIDS IN CHILDREN

BY

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Determination of the urinary excretion of 17-ketosteroids (17-oxosteroids) is the most important laboratory test in the investigation of endocrine disorders involving the adrenal cortex and gonads in children. The normal range of excretion varies with the method employed, since non-steroidal pigment may to a greater or lesser degree be measured as 17-ketosteroid. It is important therefore to know the normal range for the method used. This applies particularly to children, in whom excretion rises with age. In this paper normal values for the two most commonly used methods are given as well as figures for the commoner pathological conditions in which 17-ketosteroid excretion is raised. The evaluation of 17-ketosteroid excretion in pathological disorders is discussed.

Methods

Extraction. Twenty-four-hour urines from 73 normal children were extracted as follows. After the volume of the specimen had been measured, 100 ml. were brought to the boil on a hot-plate, and 15·0 ml. of concentrated hydrochloric acid poured down the reflux condenser. Boiling was continued for exactly 10 minutes. The urine was then cooled under the tap and extracted with 2×75 ml. and 1×50 ml. of ether. The ether extract was washed with 2×15 ml. of 10% sodium hydroxide, 1×10 ml. of a saturated solution of sodium hydrosulphite and then with water until the aqueous layer was neutral to litmus. After draining off all the water the ether was dried by adding a little anhydrous sodium sulphate and swirling. The ether was filtered (glass wool) and evaporated on a water bath using an air leak. Extracts were desiccated overnight. Each extract was then dissolved in 2·0 ml. of absolute alcohol and aliquots of 0·20 ml. removed for estimation.

Methods of Estimation. Method 1. Four tubes were set up. The first contained 0·2 ml. of extract, 0·2 ml. of 2·0% m-dinitrobenzene and 0·1 ml. of 5·0 N. aqueous potassium hydroxide; in the second tube 0·2 ml. of absolute alcohol was substituted for m-dinitrobenzene (=control); in the third tube 0·2 ml. of absolute alcohol was substituted for the extract (=reagent blank); in the fourth tube 0·2 ml. of absolute alcohol containing 50 μg. dehydroepiandrosterone was substituted for the extract. The tubes were incubated in a water bath at $25\cdot0\pm0\cdot2$°C. for 60 minutes in the dark and then to each tube was added 10·0 ml. of 70% ethanol. Readings were made in the Spekker (Hilger absorptiometer) using filter 604 and 70% alcohol as blank. Control and reagent blanks were subtracted from the reading. The amount of 17-ketosteroid present in the test was calculated by comparison with the standard reading (fourth tube) and the total for the 24-hour urine derived from this. This method of estimation has been in routine use in this hospital for many years and is similar to that of Holtorff and Koch (1940).

Method 2. In this method of estimation, which employs alcoholic in place of aqueous potassium hydroxide, the correction factor of Talbot, Berman and MacLachlan (1942) recommended by the Medical Research Council (1951) was used. To the first tube was added 0·2 ml. of extract, 0·2 ml. of 2·0% m-dinitrobenzene, and 0·2 ml. of 2·50% potassium hydroxide in absolute alcohol. Appropriate reagent blank and standard tubes were set up. After dilution with 10·0 ml. of absolute alcohol, readings of the test in the Spekker, using the green (604) and violet (601) filters were obtained and after subtraction of the blanks the corrected reading was obtained from the formula of Talbot *et al.* (1942); corrected reading $=\frac{Eg=0\cdot6\,Ev}{0\cdot72}$

Various methods of correction for non-steroidal pigments were investigated as follows:

Method 3. As in method 2, except that the Hilger Uvispek was substituted for the Spekker, readings being taken at 515 mμ. (in place of the green filter) and 425 mμ. (in place of the violet filter), the above formula being applied.

Method 4. As for method 3, but readings were made at 425 mμ., 515 mμ. and 605 mμ., and the corrected test obtained from the formula of Allen (1950), in which the corrected reading $=E\ 515-\frac{E\ 605+E\ 425}{2}$

Method 5. As in method 1 but the Hilger Uvispek was used and the corrected reading obtained as in method 4.

Results

The results for the five methods of estimation are given in Table 1. Only 57 of the 73 urines were estimated by

methods 3, 4 and 5. For convenience the means of four age groups with standard deviations are given for methods 1 and 2 in Table 2.

TABLE 1
17-KETOSTEROID EXCRETION IN NORMAL CHILDREN

Age	Method 1	Method 2	Method 3	Method 4	Method 5
weeks					
6	0·67	0·44	0·27	0·14	0·65
,,	0·32	0·23			
months					
3	0·38	0·23			
4	0·51	0·28			
,,	0·36	0·39			
8	0·37	0·10			
,,	0·37	0·21	0·00	·07	0·33
,,	0·37	0·11	0·00	0·9	0·17
years					
2	0·61	0·32	0·16	0·00	0·14
3	1·57	1·50	1·88	2·03	1·66
,,	0·34	0·23	0·02	0·00	0·07
4	2·30	1·70	0·67	0·96	1·00
,,	1·52	0·65	0·42	0·34	0·76
,,	0·75	0·35	0·17	0·06	0·27
,,	1·24	1·03	0·22	0·30	0·75
,,	2·75	1·02	0·20	0·10	0·41
,,	1·50	1·10			
5	1·76	0·77	1·24	0·96	1·40
,,	1·14	0·60	0·18	0·17	0·33
,,	1·63	0·70	0·33	0·00	0·78
,,	0·86	0·30	0·13	0·00	0·29
6	1·78	0·36	0·41	0·15	0·86
,,	2·43	1·73	0·40	0·23	1·64
,,	1·42	0·43			
,,	3·02	1·05			
7	1·10	0·97	0·70	0·48	0·92
,,	3·10	2·70			
8	1·20	0·60	0·21	0·22	0·17
,,	2·60	1·42			
,,	2·70	1·60			
,,	1·40	0·65			
,,	1·55	1·63			
,,	1·60	1·60			
9	2·06	1·50	2·00	1·50	1·00
,,	2·70	1·50	0·66	0·98	1·60
,,	2·78	2·13	1·56	1·41	1·92
,,	4·55	2·05	2·10	1·77	2·99
,,	1·11	0·50			0·16
10	2·60	0·72	1·33	1·50	0·88
,,	2·00	0·87	1·20	1·20	0·54
,,	3·55	2·10	0·60	0·41	2·80
,,	3·00	3·00			
11	3·43	3·28	2·84	2·44	2·94
,,	3·65	2·90	2·82	2·34	3·50
,,	2·60	1·72	0·14	1·05	1·24
,,	3·17	1·38	1·39	1·02	1·11
,,	5·95	4·04	4·22	1·27	3·52
,,	6·70	6·00	3·98	3·85	3·39
,,	4·25	1·95	2·28	2·15	2·30
,,	4·99	3·71	2·54	1·93	3·70
,,	5·40	4·50			
12	2·40	2·70	2·17	2·10	3·40
,,	3·71	5·38	3·21	3·46	3·43
,,	3·46	3·73	1·53	1·77	1·91
,,	9·50	8·10	7·10	6·60	6·20
,,	3·04	2·77	1·46	1·85	3·13
,,	3·48	2·75	2·26	1·70	2·80
13	8·00	5·62	5·11	4·64	4·98
,,		7·00	6·31	5·91	6·71
,,	8·30	7·15	5·50	4·88	6·30
,,	8·50	7·30	3·81	3·56	4·12
14	5·25	5·20	4·45	3·76	4·24
,,	7·11	4·75	4·89	4·40	4·25
,,	5·67	4·12	4·25	4·08	3·90
,,	8·90	8·40	5·72	4·40	7·90
,,	8·50	7·30	5·11	4·24	6·30
,,	5·30	4·50			
15	9·76	8·25	6·78	6·82	7·69
,,	7·08	7·13	6·98	6·46	8·30
,,	6·05		4·26	4·40	3·86
,,	4·34	2·71	3·07	2·77	2·85
,,	8·60	6·70	5·70	5·17	5·70
16	7·31	6·52	6·28	6·08	6·21
,,	5·72	5·30	3·48	3·48	4·31
,,	7·40	6·10	7·30	6·30	7·10

TABLE 2
MEAN EXCRETION OF 17-KETOSTEROIDS IN CHILDREN OF DIFFERENT AGE GROUPS

Age Groups (years)	Method 1 (mg./24 hr.)	Method 2 (mg./24 hr.)
0– 1	0·47± ·16	0·25± ·12
1– 5	1·38± ·66	0·78± ·46
6–10	2·30± ·85	1·38± ·74
11–17	6·03±2·14	4·96±2·06

Discussion

17-ketosteroid Excretion in Normal Children. The urinary excretion of 17-ketosteroids in children has been reported by many authors and results have varied considerably. A comparison of results by various methods has been made by Poli and Fantuzzi (1945). The results quoted for different laboratories by Dorfman (1952), all by the Holtorff and Koch (1940) method, are high compared with the results reported here. The results obtained by method 2 are in closer agreement with results reported by others who have used a similar method. Miller and Mason (1945) found averages of approximately 5·7 mg. in boys and 5·2 mg. in girls for the age group 12-17 years, while Talbot, Butler, Berman, Rodriguez and MacLachlan (1943) found an average excretion of 0·4 mg. at 5 years, and of 1·9 mg. at 10 years. Hain (1947) obtained figures for the 5-10 age group which are somewhat higher, about 3·5 mg. in boys and 2·0 mg. in girls. Bongiovanni (1951) employed aqueous potassium hydroxide, but corrected for the interfering pigments by extracting the developed colour with chloroform, and by this method obtained figures which were comparable with those of Talbot *et al.* (1943).

The three chief causes of variation are probably: (*a*) Differences in the method employed for estimating the 17-ketosteroids after extraction from the urine. (*b*) Differences in the method of extraction. (*c*) Race differences (Barnicot and Wolffson, 1952).

Only the first has been considered here. It is evident from Table 1 that the highest values are obtained by method 1, lower values with method 2, and values which are lower still with methods 5, 3 and 4 in that order. These differences are greater in the lower two age groups, illustrating that what is measured by methods 1 and 2 in these groups is to a greater extent non-steroidal pigment. The much lower results obtained by method 5, compared with method 1, is indicative of the degree to which the results are erroneously high in the latter method. Method 5 is not a valid procedure, however, because when aqueous potassium hydroxide is employed the Zimmerman reaction does not obey Beer's law. Although methods 3 and 4 give lower results than

method 2, the latter is a satisfactory routine procedure and superior to method 1. The normal range will vary according to the method of extraction employed, but differences from the results obtained here should not be great provided special purification methods, e.g. Girard's reagent, or chromatography, are not used.

Raised 17-ketosteroid Excretion in Children. The determination of the 17-ketosteroid excretion is of clinical importance in childhood in congenital adrenal hyperplasia, tumours of the adrenal cortex, and precocious puberty. It is not possible to distinguish one condition from the other by the level of excretion. In children of 5 or 6 years with hyperplasia excretion may be as little as 10 mg./24 hours (Table 3, Cases 9 and 12), or approaching 100 mg./24 hours (Table 3, Cases 13 and 32), levels which are more typical, possibly, of adenoma or carcinoma of the adrenal cortex. In all of the cases of adrenal hyperplasia (Table 3), the first 17-ketosteroid determination was abnormally high, i.e. more than the mean $+2\times$standard deviation. In Case 5, the 17-ketosteroids, determined during the first week or two of life at another hospital, were less than 1·0 mg./24 hours and this was passed as normal. It is possible therefore that very low figures may be observed in early infancy and if the diagnosis is thought probable a second specimen should be examined either immediately or in three months' time.

In congenital adrenal hyperplasia the presence of a raised pregnanetriol excretion is diagnostic, but borderline figures may occur here also in the young infant, as in Case 15, in which pregnanetriol excretion was only 0·2 mg./24 hours rising after ACTH to 0·45 mg./24 hours (Case 1, Table 4). (The mean excretion of pregnanetriol in 12 normal children of all ages was 0·04 mg./24 hours with a range of 0-0·18 mg./24 hours.) The raised 17-ketosteroid excretion was therefore of particular significance in this case, especially in view of the fact that the urogenital sinus which was present could possibly have been explained by hormone treatment which the mother had received during the early part of her pregnancy.

It sometimes happens that a child, usually 2 or 3 weeks of age, is admitted to hospital in collapse due to adrenal insufficiency associated with adrenal hyperplasia. Steroid therapy may be commenced immediately and cannot subsequently be withdrawn because of the danger of precipitating a second collapse. Urinary steroid determinations may not, therefore, be carried out, or if they are interpretation may be difficult because of the suppression of the cortex due to the administered hormones. In this event it is important to re-admit the child in order to establish the diagnosis. If suppressive treatment is withdrawn the 17-ketosteroids will be found to rise to a diagnostic level; if suppressive steroids cannot be withdrawn it may be found that the urinary pregnanetriol excretion, though partly suppressed, is still abnormally high. It is important to establish the diagnosis in a case which presents in this way because cases occur in which the plasma electrolytes are

TABLE 3

17-KETOSTEROID EXCRETION IN CONGENITAL ADRENAL HYPERPLASIA, IN BOYS WITH PRECOCIOUS PUBERTY AND IN ADRENOCORTICAL TUMOURS (ESTIMATED BY METHOD 1)

Case	Diagnosis	Sex	Age	17-Ketosteroid Excretion (mg./24 hr.)
			weeks	
1	Adrenal hyperplasia ..	M	2	5·7
2	,, ,, ...	M	4	0·9
3	,, ,, ...	M	9	4·4
4	,, ,, ...	M	10	5·0
			months	
5	,, ,, ...	M	4	7·8
6	,, ,, ...	M	4	2·7
7	,, ,, ...	M	7	8·0
			years	
8	,, ,, ...	M	5	22·7
9	,, ,, ...	M	5	10·3
10	,, ,, ...	M	5	25·3
11	,, ,, ...	M	6	16·9
12	,, ,, ...	M	6	9·1
13	,, ,, ...	M	6½	78·9
14	,, ,, ...	M	9	38·8
			weeks	
15	,, , ...	F	4	2·2
16	,, ,, ...	F	4	3·7
17	,, ,, ...	F	4	7·7
18	,, ,, ...	F	6	3·9
19	,, ,, ...	F	6	7·5
20	,, ,, ...	F	8	5·3
21	,, ,, ...	F	8	4·9
22	,, ,, ...	F	8	2·5
			months	
23	,, ,, ...	F	5	3·9
24	,, ,, ...	F	6	3·8
25	,, ,, ...	F	7	6·4
26	,, ,, ...	F	11	2·8
27	,, ,, ...	F	18	12·6
28	,, ,, ...	F	18	3·1
			years	
29	,, ,, ...	F	2	6·2
30	,, ,, ...	F	4	40·3
31	,, ,, ...	F	5	20·3
32	,, ,, ...	F	8½	29·1
	,, ,, ...	F	10½	129
			months	
33	Precocious puberty ..	M	11	0·3
			years	
34	,, ,, ...	M	3	2·4
35	,, ,, ...	M	4	2·7
36	,, ,, ...	M	10	8·9
37	Adrenocortical adenoma (with virilism)	F	6	3·4—7·5
38	,, ,, ,, ..	F	10	10·0
39	,, ,, ,, ..	F	2	4·1—6·0
40	,, ,, ,, ..	F	5	17·2—20·7
41	Adrenocortical carcinoma (with virilism)	M	2	120 —263
42	Adrenocortical adenoma (with Cushing's syndrome)	M	3	4·2
			months	
43	Bilateral adrenocortical multiple adenomata (with Cushing's syndrome) ..	F	14	3·0

TABLE 4

17-KETOSTEROIDS AND PREGNANETRIOL EXCRETION BEFORE AND AFTER ACTH 10 mg./24 HOURS (CASE 1) AND 40 mg./24 HOURS (CASES 2, 3 AND 4) FOR THREE DAYS

	Case 1	Case 2	Case 3	Case 4
	(*values in mg./24 hr.*)			
17-ketosteroid				
before ACTH ..	2·2	7·3	7·7	30·1
after ACTH ..	3·5	13·8	23·4	39·7
Pregnanetriol				
before ACTH ..	0·2	20·5	14·0	20·0
after ACTH ..	0·4	15·0	37·0	36·8

typical of adrenal insufficiency, though there is no confirmatory evidence of this. In two such cases, both boys, aged 5 and 9 weeks of age, the 17-ketosteroids were raised and subsequently fell. The figures in mg./24 hours were 1·10; 0·85; 0·81; 0·56; and 1·80; 1·13 and 1·00 respectively. It is possible that the 17-ketosteroids were raised as a result of the illness. Such cases might be diagnosed incorrectly as having congenital adrenal hyperplasia. While a provisional diagnosis of hyperplasia can be made on the basis of abnormal plasma electrolyte levels in male infants, and on the presence of a urogenital sinus with or without associated abnormal plasma electrolyte levels in girls, a definitive diagnosis can only be made by the investigation of urinary steroid excretion.

In boys with precocious puberty the 17-ketosteroids may be raised to levels characteristic of the physiological age but are unlikely to exceed 10 mg./24 hours. If 17-ketosteroid excretion is less than 10 mg. a day in a boy, the distinction between the virilizing tumour and precocious puberty must be made on clinical grounds. A raised gonadotrophin excretion would support a diagnosis of precocity, and in adrenocortical tumours the testes are likely to be normal in size for the chronological age. A diagnosis cannot be established on those grounds, however, and special investigations will be required to exclude a tumour.

ACTH tests are of little importance in the diagnosis of congenital adrenal hyperplasia. After administration of ACTH, 20 mg. b.d. for three days, pregnanetriol excretion in a normal child was 0·4 mg./24 hours on the third day. In adrenal hyperplasia pregnanetriol and 17-ketosteroid excretion usually rise after ACTH administration, but this is not invariable (Table 4).

Summary

The excretion of 17-ketosteroids by normal children and by children with congenital adrenal hyperplasia, adrenocortical tumours, and with precocious puberty has been determined. The clinical evaluation of 17-ketosteroid excretion is discussed.

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THE URINARY EXCRETION OF 17-HYDROXYSTEROIDS IN CHILDREN

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From The Hospital for Sick Children, Great Ormond Street, London

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The results reported here were obtained as a consequence of routine requests for steroid estimations. Some of the normal figures were obtained privately, but others were obtained from children in hospital, who had no endocrine wasting or similar disorder likely to influence adrenocortical secretion. Most of the requests concerned four types of case: obesity, dwarfism, precocious puberty and adrenal hyperplasia or tumour.

Method

The method of Reddy (1954) was employed. This measures those corticosteroids which have a 17:21-dihydroxy-20-ketone side chain. The two principal glucocorticosteroids which are secreted by the adrenal cortex are hydrocortisone (approximately 85%) and corticosterone (approximately 15%) (Bush, 1953). The principal corticosteroids present in urine are hydrocortisone, cortisone and their metabolites. Both hydrocortisone and cortisone possess the 17:21-dihydroxy-20-ketone side chain, so also do their principal metabolites and therefore these compounds will be measured by the method. Corticosterone lacks the 17-hydroxyl group and it is not measured by this method.

Results

The 17-hydroxysteroids were determined in the 24-hour urines from 94 normal children. The children were divided into two groups, those under 2 years of age, and those over 2. This was done principally because few results were obtained for children at about the age of 2, a most difficult age at which to obtain 24-hour specimens of urine from normal children. The mean excretion of 17-hydroxysteroids in the younger age group was $1{\cdot}2\pm1{\cdot}0$ mg./24 hours. In the older group the mean excretion was $3{\cdot}1\pm2{\cdot}0$ mg./24 hours (Table 1). The difference between the two groups is highly significant ($P<{\cdot}01$). There is no significant difference between the mean figures for excretion for the ages 0-1 year and 1-2 years and the results may be considered as falling into one group. There is probably a rise with age in the older group but the regression is not significant.

Results were obtained from 23 cases of obesity, all of whom were in the older age group. The mean excretion was 3·4 mg./24 hours. In three cases of dwarfism in the younger age group the mean excretion was 0·9 mg./24 hours, and in 15 cases in the older age group it was 2·1 mg./24 hours. In five cases precocious puberty in the earlier age group the mean excretion was 0·7 mg, and in five cases in the older group it was 3·8 mg./24 hours. None of these figures is significantly different from the normal.

TABLE 1

URINARY 17-HYDROXYSTEROID EXCRETION IN NORMAL CHILDREN

Age Last Birthday (years)	Mean 17-hydroxysteroid Excretion (mg./24 hr.)
0– 2	$1{\cdot}2\pm1{\cdot}0$
2–17	$3{\cdot}1\pm2{\cdot}0$

In the syndrome of congenital adrenal hyperplasia, the excretion of 17-hydroxysteroids is low when determined by paper chromatography (Eberlein and Bongiovanni, 1955). The Reddy method, however, indicates the excretion of normal levels of 17-hydroxysteroids, though in two cases, in brothers, excretion was persistently zero. Furthermore, in three cases to whom ACTH was administered levels rose (Table 2). It must be concluded therefore

TABLE 2

17-HYDROXYSTEROID EXCRETION IN 15 CASES BEFORE AND AFTER ACTH 40 mg./24 HOURS FOR THREE DAYS

Case No.	Diagnosis	Age (years)	17-hydroxysteroids Before ACTH (mg./24 hr.)	17-hydroxysteroids After ACTH (mg./24 hr.)
1	Normal	9	4·3	18·1
2	,,	6	8·8	56·5
3	Dwarfism	1	1·3	11·2
4	,,	5	0·0	8·2
5	,,	6	2·1	17·4
6	,,	6	4·8	41·9
7	,,	6	1·6	26·8
8	,,	8	3·5	26·1
9	,,	8	2·9	20·9
10	,,	10	4·1	24·2
11	,,	11	2·7	31·6
12	,,	13½	1·3	9·6
13*	Congenital adrenal hyperplasia	4 *weeks*	2·6	4·7
14	,, ,,	2	2·3	9·6
15	,, ,,	6½	2·7	12·7

* In Case 13, ACTH 10 mg./24 hours was administered. The highest figures before and after ACTH are given.

that the compounds measured in this condition are not the same as the compounds excreted by normal subjects.

In six children with dwarfism an ACTH test was carried out. A base line figure was obtained for one or two days prior to the test, and ACTH, 20 mg. b.d. was then administered for three days. Table 2 shows the base line figures and the highest figure obtained after ACTH. Excretion usually declined to the control level on the second day after the last dose of ACTH.

The administration of cortisone will cause a rise in 17-hydroxysteroid excretion. In four adults, 50 mg. of cortisone acetate was administered at 8 a.m. and again at 6 p.m., and the 24-hour urine collection commenced at 8 a.m. on the same day. The excretion of 17-hydroxysteroids by the four individuals was 28·8 mg., 28·2 mg., 26·4 mg. and 24·2 mg. The mean base line figure was 2·4 mg./24 hours.

The 17-hydroxysteroids were determined for the first 19 days after menstruation in a girl aged 11 years. The figures in mg./24 hours were 3·3, 4·3, 14·4, 5·6, 4·3, —, 7·4, 7·7, 7·1, 7·8, —, 7·3, 7·6, 9·5, 9·0, 7·0, 6·0, 7·2, 6·7. It will be observed that, except for the high figure obtained on the third day for which there was no obvious explanation, the level of excretion rises to a peak of 9·5 mg./24 hours, and then declines. This peak of excretion occurred on the day following the peak of oestrogen excretion which was determined concurrently.

In a case of Cushing's syndrome in a boy aged 3½ years, the 17-hydroxysteroids were 3·1 mg./24 hours. In a second case due to bilateral adrenal multiple adenomata, the 17-hydroxysteroids were 9·8 mg./24 hours.

Discussion

The method of Reddy is simpler to perform than the 17-ketogenic method of Norymberski, Stubbs and West (1953). The latter method involves the simultaneous determination of the 17-ketosteroids, but since this result is usually required this is a gain rather than otherwise. In this hospital, however, a method similar to the method of Holtorff and Koch (1940) but different from that employed in the determination of 17-ketogenic steroids has been in use since 1940. An independent method of 17-hydroxysteroid determination was therefore of value. Reddy (1954) gives the normal adult range of 17-hydroxycorticosteroids as 1·1-10·7 mg./24 hours with a mean of 4·7. The smaller excretion in children must be due to size, since blood levels are similar (Ely, Raile, Bray and Kelley, 1954). It is of some importance that the upper limit of normal is lower in children since in Cushing's syndrome the figures may be only moderately raised, or, as in one of the cases referred to here, within the normal range. The difficulties of interpretation of ACTH tests have been discussed by Prunty (1956). Since it is not permissible to experiment with normal children by administering ACTH it is hardly possible to obtain genuine controls, and only two cases to whom ACTH had been given therapeutically were considered to be normal controls (Table 2). The response in Case 2 is striking, and it is of interest that the base line figure here is high. The 17-ketogenic steroids after ACTH in this normal child reached 70 mg./24 hours, a figure which matches the response to ACTH in the cases of Cushing's syndrome due to adrenal hyperplasia described by Prunty.

In the cases of dwarfism (who were given ACTH from the same batch) it is clear that the response is variable, though it is possible that the response varies directly with the base line figures.

The normal excretion of 17-hydroxysteroids in one of the cases of Cushing's syndrome (the 17-ketosteroids were moderately raised) reveals the limitations of laboratory methods in this condition. Since in children tumours of the adrenal cortex and not hyperplasia are usually the cause of the syndrome, it is probably true that laboratory investigations can confirm the clinical diagnosis but cannot exclude it.

The 17-hydroxysteroids may also be of value in the diagnosis of Addison's disease and an ACTH test is of importance here. Otherwise it may be concluded that apart from Cushing's syndrome and Addison's disease, both rare disorders in childhood, the clinical value of 17-hydroxycorticosteroid determinations is limited.

Summary

The urinary excretion of 17-hydroxysteroids by normal children and by children attending hospital for obesity, dwarfism, precocious puberty and adrenal hyperplasia has been determined. The clinical value of this determination is discussed.

We wish to thank the physicians and surgeons of The Hospital for Sick Children, Great Ormond Street, for permission to study their cases, and the Research Committee for their support.

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THE PROGNOSIS IN JUVENILE OBESITY

BY

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Juvenile obesity is common. Probably few paediatricians or general practitioners regard it as a serious medical problem. It has not been shown to be associated with high mortality or morbidity rates and, except in the most extreme cases, it is widely regarded as a benign if unsightly condition, usually associated with excessive eating and with tendencies both to improve and to persist. Recently the psychiatric aspects of the condition have aroused interest, and extensive studies have been published (Bruch, 1939, 1940, 1941, 1957; Juel-Nielsen, 1953; Iversen, 1953; Østergaard, 1954).

The exact incidence of juvenile obesity in this country is not known. Johnson, Burke and Mayer (1956) studying a cross-section of elementary and secondary schoolchildren in Boston, found that it occurred in 9% of the boys and in 12·5% of the girls in 6,000 children. It is doubtful whether the incidence is as high in this country. There is evidence that in some parts of the world its incidence is rising. In Germany, Haase and Hosenfeld (1956) found that, whereas its incidence fell enormously during the war, there are now five times as many cases seen in their clinic as in 1939.

A search of the literature failed to reveal any investigation of the ultimate dangers of juvenile obesity.

Obesity in adults is now one of the greatest medical problems in the western world and its dangers have been intensively studied. Obesity is known to shorten the life of animals (McCay, Maynard, Sperling and Osgood, 1941; Hansson, Brännäng and Claesson, 1953; Kennedy, 1951, 1955). For a long time insurance companies have known that among adults accepted for life insurance overweight of all degrees and at all ages is associated with a high mortality and morbidity. The subject has recently been reviewed by Armstrong, Dublin, Wheatley and Marks (1951) and by Marks (1956). Dublin (1953) points out that the relative increase of mortality in the overweight is increasing, since diseases in which mortality is higher in the underweight, chiefly pulmonary tuberculosis and pneumonia, are declining.

Probably the mortality of the obese as a class is even higher than insurance statistics suggest, since the subjects from whom the statistics were obtained were chosen as good insurance risks (Evans, 1952). Sinclair (1954) has said that if you are in middle life or more, your chances of dying early are greater if you are 10 lb. overweight than are your chances of getting carcinoma of the bronchus if you are a heavy smoker. Jolliffe (1953) calculated that if a cure were found for carcinoma, the average life expectancy would be increased by two years, whereas if obesity were cured, it would be increased by four years.

The part played in this state of affairs by persistent juvenile obesity has not been worked out. Few long-term results of treatment in this condition have been published, and authorities differ in their opinions. Gurney (1936) studied 63 fat women and found that eight of them had been obese all their lives and a further four since puberty; thus persistent juvenile and pubertal obesity existed in approximately 19% of his cases. Ellis and Tallerman (1934) state: 'It is well known that the majority of obese children tend to gravitate toward the normal after puberty has been reached.' Le Marquand (1951) found that a large proportion of fat girls traced to adult life either remained fat or became fat again after childbirth. Bornhardt (1936) re-investigated 65 obese children while they were in their teens and found that girls tended to remain obese more frequently than boys. Mossberg (1948) followed up 328 patients who had been admitted to hospital for obesity in childhood and found that the prognosis was worse in girls than in boys. Hering (1938) re-investigated 30 patients, and found that 10 were normal, 10 were 'giants',

i.e. both tall and overweight but without giving an impression of obesity, and 10 were still obese. Hässler (1935) obtained similar results. Haase and Hosenfeld (1956) followed up 21 boys and 24 girls who had been treated before the war, and found that in most of them the condition had persisted. Some of them had lost weight at puberty or during the war, but of these, most had again become obese.

Object of Present Work

This investigation was done because, whilst it was observed that obesity is very common among adult hospital medical out-patients and was either directly responsible for their symptoms or exacerbated the diseases for which they attended, the treatment of the condition was only successful in a minority of cases. In view of this it seemed important to study the subject, and to attempt to discover how far obesity in later life is due to persistent juvenile obesity.

Material and Method

The age, sex, height and weight were recorded in 373 patients seen consecutively in the medical out-patient department at St. James' Hospital, Balham, and the results were compared with the standard tables of Kemsley (1952).

One hundred and one patients seen in out-patients who were 20% or more overweight were selected for further study. These are the 'obese' group, and were sub-divided into 'juvenile obese' and 'adult obese' groups according to whether or not they had been known as 'fatty' at school; this was found to be the most practical single criterion.

Fifty patients whose weight was within 20% of normal weight were studied in a similar way. They were chosen primarily for co-operation and intelligence. An attempt to take detailed life and dietary histories from an unselected series of out-patients of normal weight was abandoned and it was decided that, in spite of the differences between the two groups, intelligent and co-operative subjects would provide more valuable information which could later be used for more standardized studies. Thus the two groups can be compared in some respects, but the 'normals' cannot be regarded as 'controls'.

Twenty-one adults who had received medical treatment for obesity during childhood were investigated in the same way, special attention being paid to possible reasons why their obesity had persisted or resolved. This is the 'treated juvenile obese' group.

Seven patients in the 'treated juvenile obese' group and three in the normal group had suffered from juvenile obesity and later become normal. These were classed together as the 'normal juvenile obese' group.

Each patient was asked the history of her weight and its relation to her life-circumstances. An attempt was made to assess her appetite and type of diet and the factors influencing these. Special attention was paid to early and family history, the influence of pregnancy, and to possible medical and psychological factors influencing the condition. In addition, the usual medical history was taken, a full clinical examination was done in every case and any investigations thought necessary were carried out.

An attempt was made to treat all these patients as out-patients. The method of treatment was primarily dietary with the object of accustoming the patients to a bulky low-calorie diet and of re-educating their eating habits rather than of producing rapid and temporary loss of weight. Drugs, chiefly dextroamphetamine sulphate, were used when it did not seem possible to treat the patient by dietary means alone.

Overall Results

Incidence of Overweight. The impression that obesity is common among the patients was confirmed (Fig. 1). Of the 373 medical out-patients 36% of the men and 52% of the women were more than 10% above standard weight. Twenty-six per cent of the men and 44% of the women were

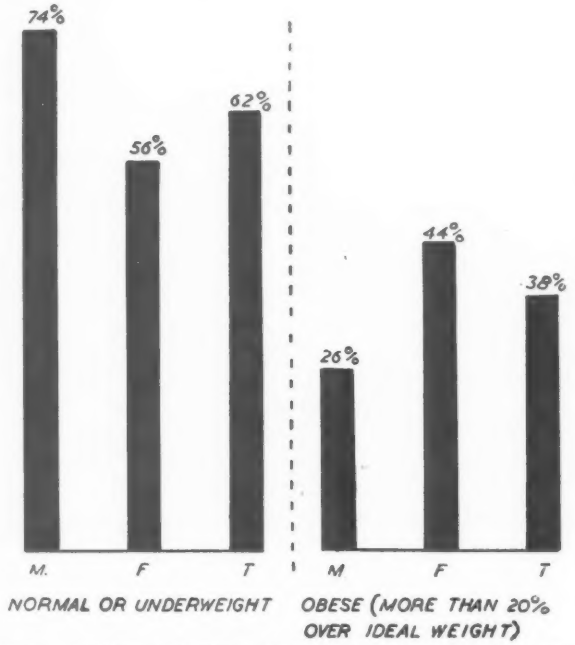

FIG. 1.—Incidence of obesity in 373 medical out-patients. M. = Male; F. = Female; T. = Total.

more than 20% above standard weight, and so were classed as 'obese'. It is interesting to note that a higher percentage of the women (21%) than the men (14%) were also underweight, and that only 26% of the women, compared with 51% of the men were within 10% of standard weight.

Obese Group. Table 1 shows the distribution of age, sex and type of obesity in the 101 obese patients. Of these approximately one third were cases of persistent juvenile obesity and in the remaining two thirds the obesity developed later in life.

TABLE 1

DISTRIBUTION OF 101 OBESE PATIENTS ACCORDING TO AGE, SEX AND TYPE OF OBESITY

Age (years)	Juvenile Obese (32)			Adult Obese (69)			Totals (101)		
	M.	F.	T.	M.	F.	T.	M.	F.	T.
18–19 ..	–	2	2	–	–	–	–	2	2
20–29 ..	–	3	3	3	1	4	3	4	7
30–39 ..	–	2	2	–	6	6	–	8	8
40–49 ..	3	6	9	4	13	17	7	19	26
50–59 ..	–	12	12	9	13	22	9	25	34
60–69 ..	2	2	4	2	11	13	4	13	17
70–79 ..	–	–	–	2	5	7	2	5	7
Total ..	5	27	32	20	49	69	25	76	101

Table 2 and Fig. 2 record the severity of the obesity in the obese group, and show that the condition tended to be more severe in the juvenile obese group than in the adult obese group.

It was not possible to discover the age at onset of the obesity in all the relatives, but the impression gained from those who could remember was that the obese husbands and wives of the obese group tended to become obese after marriage, and that the obese daughters of obese women tended to become obese at the same age as their mothers. There were, however, exceptions to this and one case was seen in which obesity developed rapidly in both mother and son simultaneously.

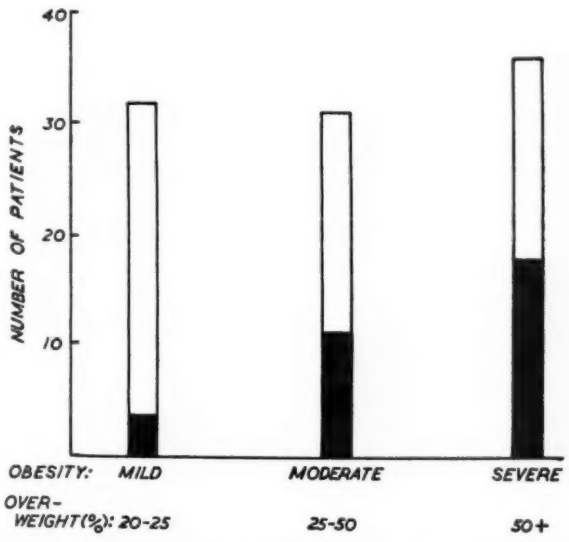

FIG. 2.—Histogram showing proportion of juvenile-type obesity in 101 obese patients. ■ Juvenile obese. □ Adult obese.

TABLE 2

SEVERITY OF OBESITY IN 101 OBESE PATIENTS

Severity	Juvenile Obese (32)				Adult Obese (69)				Totals (101)		
	M.	F.	T.	%	M.	F.	T.	%	M.	F.	T.
Mild (20%–25% overweight)	–	4	4	12	10	18	28	41	10	22	32
Moderate (25%–50% overweight)	3	8	11	35	7	14	21	30	10	22	32
Severe (more than 50% overweight)	2	15	17	53	3	17	20	29	5	32	37

Family History. Table 3 and Fig. 3 show the incidence of obesity in the families of the obese and normal groups. Obesity occurred more frequently in the near relatives of the juvenile obese group than in the adult obese group. In the normal group there was a lower incidence of obesity among all the relatives, and this was most marked in the father and spouse. Fifty per cent of the juvenile obese group had obese fathers compared with only 2% of the normal group, and 22% of the juvenile obese group were married to obese people compared with 4% of the normal group.

Influence of Pregnancy and Menopause. It is well known that women tend to become obese during pregnancy and at the menopause and that those who are already obese tend to become more obese at these times (Gurney, 1936; Greene, 1939; Sheldon, 1949; Richardson, 1952). It has also been observed (Sheldon, 1949; Richardson, 1952) that women who were overweight at marriage were more likely to gain excessive weight due to deposition of fat during pregnancy, than those whose weight was normal at marriage. It might therefore be expected that women with persistent juvenile

obesity tend to become even more obese with pregnancy. The present findings do not appear to confirm this (Table 4). Only 44% of the juvenile obese group compared with 72% of the adult obese group and 53% of the normal group gained weight excessively in pregnancy, and afterwards had to wear clothes of a larger size. The numbers are small, but if the difference is real it does not necessarily conflict with the findings of Sheldon and Richardson. In a recent personal study of maternal obesity it was found that those who were overweight at marriage were prone to develop maternal obesity, but even more prone were those who had been overweight at some time before marriage and had reduced their weight. The difference was accounted for by those who had never tried to reduce their weight, among whom the incidence of maternal obesity was low. Although the exact age of onset of the obesity was not recorded, it is possible that these were cases of persistent juvenile obesity.

Only two women (7%) in the juvenile obese group had gained excessive weight at the menopause, compared with 12 (25%) of the adult obese group.

The figures suggest, therefore, that persistent juvenile obesity increases less during the physio-

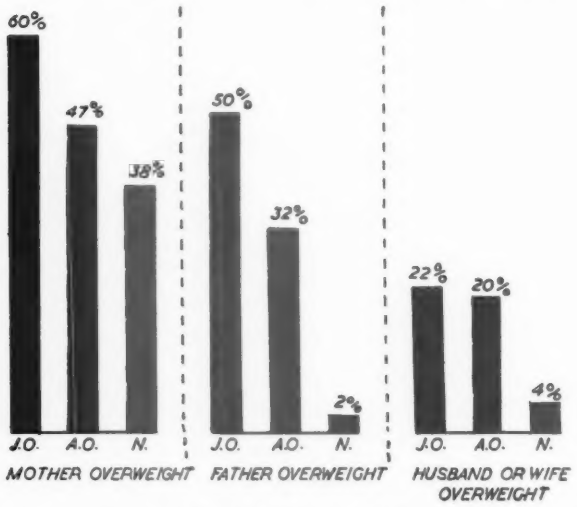

FIG. 3.—Incidence of obesity in parents and spouses of 101 obese patients and 50 patients of normal weight.
J.O.=Juvenile obese; A.O.=Adult obese; N.=Normal.

TABLE 3
FAMILY HISTORY OF OBESITY IN 101 OBESE PATIENTS COMPARED WITH 50 PATIENTS OF NORMAL WEIGHT

Relative	Juvenile Obese (32)		Adult Obese (69)		Totals (101)		Normal Group (50)	
	No.	%	No.	%	No.	%	No.	%
Mother:								
Overweight	20	62	32	46	52	51	19	38
Normal	11	34	27	39	38	38	26	52
Father:								
Overweight	16	50	22	32	38	38	1	2
Normal	14	44	34	49	48	48	43	86
One or more sisters:								
Overweight	15	47	28	41	43	43	14	28
One or more brothers:								
Overweight	13	41	22	32	35	35	2	4
Husband or wife:								
Overweight	7	22	14	20	21	21	2	4
Normal	18	56	36	52	54	53	35	70

The apparent discrepancies in the figures are due to patients who could not remember their parents or who were not married.

TABLE 4
EXCESSIVE WEIGHT GAIN IN PREGNANCY IN 101 OBESE PATIENTS COMPARED WITH 50 PATIENTS OF NORMAL WEIGHT

	Parous Women in Groups: Juvenile Obese (18)		Adult Obese (36)		Normal (30)	
	No.	%	No.	%	No.	%
Excessive weight gain* in pregnancy	8	44	26	72	16	53
No excessive weight gain† in pregnancy	8	44	10	28	14	47
No recollection	2	12	—		—	
Weight became normal after pregnancy associated with excessive weight gain	0/8	0	2/26	8	16/16	100
Excessive weight gain at menopause	2/27	7	12/49	25	Not recorded	

* i.e. wore larger clothes after pregnancy. † i.e. wore same size of clothes after pregnancy.

logical changes of pregnancy and the menopause than other types of obesity.

Types of Appetite. Most authorities stress the alimentary cause of juvenile obesity. Østergaard (1954) found that none of his control group with large appetites gave the impression of eating urges comparable with those found in some of his obese group. Kerley and Lorenze (1941) state: 'These children are alike in possessing habitually insatiable appetites and a capacity for excessive food intake without resulting illness'. They also found that obese children had a preference for sweet and starchy foods.

In the juvenile obese group, 25 patients (78%) admitted to large appetites, and their replies were substantiated by further questions as to food intake. This compared with 28 (41%) of the adult obese group and 14 (28%) of the normal group. A preference for sweet, starchy and fried foods was common among the obese, but the normal subjects with large appetites usually ate bulky and savoury foods in preference to sweet, though they too mostly liked fried foods.

It is well recognized that psychological factors can play a large part in the aetiology of obesity. The frequency with which they are said to occur varies according to the worker, the criteria and the selection of patients. Bruch (1940), studying obese children in hospital practice, found that specific psychological factors were the most important in the production of obesity. Juel-Nielsen (1953) found psychological difficulties in nine out of 60 obese schoolchildren, and Iversen (1953) in 16 out of 40. Both these workers found that the psychological factors were less specific than in Bruch's series.

Psychiatric histories taken in the present series were no more detailed than those taken by any careful physician except that their possible connexion with appetite and food intake was carefully noted. Psychological factors that appeared to lead to increased food intake were found on the first interview in 17 (53%) of the juvenile obese group, 34 (49%) of the adult obese group and nine (18%) of the normal group. The patients were found to be of two main types:

(1) Those who normally reacted to worry and nervous tension by increase of food intake. This was by far the commonest type (Table 5). Probably most people, both normal and obese, react to stress by decrease of appetite and, if the stress is prolonged, by loss of weight. It is recognized, however, that some people react to mild and sometimes even to severe stress by increased food intake. Johnson (1947) quotes an interesting case of a thin husband and a plump wife submitted to the same psychological stress. The husband lost 13 lb. in weight and the wife gained 26 lb. before their worry ended. Freed (1947) asked 500 patients under treatment for obesity whether they ate more when nervous or worried; 370 (74%) answered 'yes'. The patients in the present series were asked the same question (Table 5). The incidence among the obese is much lower than in Freed's group, but it is nevertheless high, and is higher in the juvenile obese than in the other groups. Many patients admitted freely to this reaction and were well aware of it; others had not previously thought about it, but on being questioned they admitted that overeating was their usual reaction to stress. The overeating was usually non-specific, though in a few patients a specific craving for a particular food occurred and their descriptions of this sounded very much like the pica that is known to occur in pregnancy, and sometimes seemed to be associated with it.

TABLE 5

INFLUENCE OF WORRY AND PSYCHOLOGICAL STRESS ON APPETITE IN OBESE AND NORMAL PATIENTS

Effect of Stress on Appetite	Juvenile Obese (32)		Adult Obese (69)		Normal Group (50)	
	No.	%	No	%	No.	%
Increased	14	44	18	26	9	18
Decreased	8	25	20	29	31	62
Unaffected	10	32	31	45	10	20

M.J., aged 38 and 74% overweight, had been obese all her life and had increased markedly in weight during three pregnancies. Her father, mother, husband and daughter were all obese. Since childhood she had had a craving for milk chocolate which she tried to control. Normally she managed to restrict herself to ¼ lb. a week, but when worried or pregnant she could not pass a sweet shop without buying a bar and during these times ate at least ½ lb. every day.

It is interesting to note that the excessive eating reaction to stress was found in only 9 (18%) of the normal group.

(2) The second group were those in whom obesity developed or increased rapidly in association with a specific psychological trauma. Shorvon and Richardson (1949) described six such cases in adults. Østergaard (1954) describes obesity in children associated with a death in the family, separation of the parents or the birth of a baby. Three patients (9%) in the juvenile group and 13 (19%) in the adult group were of this type. It is probable that a

specific trauma of this kind is less likely to be recalled if it occurred in childhood than in adult life.

Results of Treatment

Bruch (1955) and Stuart (1955) found that obesity which had developed in childhood was particularly difficult to treat. The results of treatment in the obese group confirm these findings.

The criteria of success were:

(1) Poor. This group includes patients who failed to lose more than 30% of their excess weight during at least four months' treatment, and those who, within this time and before any success had been achieved, ceased to attend the clinic.

(2) Moderate. This group includes those who, during treatment lasting at least four months, lost more than 30% of their excess weight but who did not reduce their weight to within 20% of standard weight, or, in cases of mild obesity, to within 10% of standard weight.

(3) Good. This group includes all patients who reduced to within 10% of standard weight and all patients with moderate or severe obesity who reduced to within 20% of standard weight.

(4) Not yet known. This group includes all patients who had been under treatment for less than four months and who were still attending at the time of writing.

Most of the patients in groups (2) and (3) are still under treatment, and therefore it is hoped that the ultimate results will be better.

The results of treatment are shown in Table 6.

TABLE 6
RESULTS OF TREATMENT OF OBESITY

Result of Treatment	Juvenile Obese (32)		Adult Obese (69)	
	No.	%	No.	%
Poor	20	62	27	39
Moderate	8	25	17	25
Good	0	0	10	14
Not yet known	4	13	15	22

The incidence of failure is much higher in the juvenile type than in the adult type. So far, treatment has not resulted in complete success in a single case in the juvenile group. However, the fact that a quarter of them have lost more than 30% of their original excess weight is hopeful, since all these patients are still under treatment. The fact that, not only the incidence, but also the degree of success appears to be greater in the adult than in the juvenile group may be due to the higher incidence of severe obesity in the juvenile group and, therefore, the longer time necessary before complete success is achieved. Nearly all the patients in whom some success has been achieved are still attending the clinic at the time of writing.

A common difficulty in treating obesity is the appearance of new symptoms which appear to be related to the diet. Symptoms of hunger, mild depression and constipation are so common that they can be expected. *Severe reactions*, however, also occur, and, if they are not successfully treated, usually herald the failure of treatment, and the patient's failure to keep further appointments. Common among the more severe reactions are uncontrollable hunger and craving for food, severe depression, hysterical outbursts, flatulence, abdominal pain, an overwhelming preoccupation with bowel action, headaches, giddiness, faintness, nightmares and bizarre symptoms. Severe reactions occurred in nine patients (28%) of the juvenile group and in seven patients (10%) of the adult group who continued to attend the clinic (Table 7). It is probable that they were the cause of failure in some other patients to attend the clinic. When psychological complications were absent, severe reactions occurred in about a fifth of both juvenile and adult obese groups. When the complications were present, however, though severe reactions were twice as frequent in the juvenile obese, in the adult obese group they occurred only half as commonly as in the adult obese without psychological complications. The adult obese group with obvious psychological complications were more amenable to treatment than those without, whereas in the juvenile group the situation is reversed. Since these reactions often lead to failure to keep appointments, and the incidence of failure is also higher

TABLE 7
INCIDENCE OF SEVERE PSYCHOLOGICAL REACTIONS TO TREATMENT IN 101 OBESE PATIENTS

	Juvenile Obese			Adult Obese		
	No.	Reactions	%	No.	Reactions	%
All patients	32	9	28	69	7	10
With apparent psychological factors	17	6	35	34	2	6
Without apparent psychological factors	15	3	20	35	5	15

in the juvenile group, it seems likely that these reactions are an important cause of the higher incidence of failure in the treatment of the juvenile group.

Since most of these patients are still under treatment, it is probable that the ultimate incidence of severe reactions occurring among them will be higher than at present recorded.

Treated Juvenile Group. Of 21 adult patients who had been under medical care for obesity in childhood, 10 were still obese, and most of these were severely obese. Four were exceptionally tall and overweight, but not obese, and seven (five females and two males) were of normal height and within 20% of normal weight. The findings agree in the main with those of other workers (Bornhardt, 1936; Hering, 1938; Mossberg, 1948; Le Marquand, 1951; Haase and Hosenfeld, 1956).

Of the 10 patients who were still obese, four had lost weight during treatment in childhood, but none had become normal. The remaining six had not lost weight. Five of the group, as far as could be ascertained from the records, had failed to keep further appointments, presumably due to parental influence. The four patients who had grown exceptionally tall had not responded to treatment in childhood but all stated that they ceased to be obese during a later period of rapid growth, and in three of them this coincided with markedly increased activity.

Normal Juvenile Obese Group. In the 10 patients who had been under medical care for obesity in childhood and whose weight as adults was within 20% of normal weight there were several outstanding features:

(1) All these patients were at least 5% above standard weight, and none of them had ever been below it.

(2) With one exception they were all highly intelligent, compared with most other patients attending the hospital. Nine of the 10 (90%) had had a grammar school education. Among the 101 patients in the 'obese' group, only six (6%) had had a grammar school education and a large number appeared to be of very low intelligence. Only one of the 'treated juvenile obese' group who had remained obese had been to a grammar school.

Dorff (1935) found that obese children tended to be retarded. Bronstein, Wexler, Brown and Halpern (1942) found that the mean intelligence of obese children was higher than the mean of the general population, but found a tendency among them to be of either superior or retarded development. Østergaard (1954) found a normal distribution of intelligence among obese children and agreed with Bruch (1940) that serious obesity occurs less frequently under good social conditions than poor. In all the patients seen during the present investigation, there has been no case of severe obesity who had had a grammar school education, and, before the outstanding incidence of high intelligence in children who became normal was realized, a strong clinical impression was formed that the degree of success achieved in the treatment of adults was closely related to the intelligence of the patient.

(3) The mothers of these patients were intelligent and co-operative, and those who were themselves overweight (seven out of 10) made strong and successful, if sometimes intermittent, attempts to control their own weights.

(4) Weight reduction is associated with increased activity. In some cases increased activity followed weight reduction by dietary means. In others it seemed to occur spontaneously.

Discussion and Conclusion

Every case of obesity is 'exogenous' in that it is due to an intake of calories greater than the amount required for standard body weight. It can be argued that every case of obesity is 'endogenous' in that the cause for the excessive intake lies within the patient. Every case of obesity can be cured by reduction of caloric intake relative to the body's needs. Yet, in a very high proportion of cases, the condition seems untreatable by the methods in common use because the patient continues to eat in excess of the amount required for weight loss. Since this depends far more on the patient than on the doctor, a sense of hopelessness is easily induced in the minds of physicians attempting to treat the condition. Nevertheless its dangers make it important to increase our knowledge and to attempt to treat the condition whenever it is seen.

Approximately one third of all patients attending medical out-patients were found to be obese and, of these, approximately one third were found to be cases of persistent juvenile obesity. Thus more than 10% of medical out-patients had been obese from childhood. These patients did not on the whole appear to differ qualitatively from the other obese patients, but they tended to be more severely obese and a higher incidence of factors known to be associated with obesity was found among them, including large appetites, a family history of obesity and a tendency to eat more when nervous or worried.

Periods of endocrinological change, such as pregnancy and the menopause, appeared to have less influence on their weights than on those of the adult obese group.

The most marked difference between the two groups was in the results of treatment, which was much less successful in those whose obesity dated from childhood. This seemed to be at least partly due to the higher incidence of failure to keep appointments and of severe reactions to treatment in the juvenile obese group.

It is of interest that in the adult obese group treatment was more successful and the incidence of severe reactions was lower in those with obvious psychological factors complicating the obesity than in those who appeared normally adjusted. The reverse is the case in those whose obesity has been present since childhood.

In considering those patients who had suffered from juvenile obesity and who later became normal, the outstanding difference between them and those who remained obese lay in their intelligence. This finding confirmed a previous impression that intelligence is an important factor in the prevention of obesity and in the success of treatment. The present findings suggest that the usual methods of treatment are adequate for most intelligent obese children, but inadequate for the less intelligent, and it is felt that this is probably true for most adults too. The obese adult of low intelligence who has been obese since childhood or who has become addicted to food in later life is probably the most difficult of all patients to treat for obesity.

It is concluded that persistent juvenile obesity is an important cause of obesity in adult life and is, therefore, a potentially dangerous condition.

Juvenile obesity that persists into adult life tends to be more severe and more difficult to treat than obesity occurring in adult life.

Psychological factors play a larger part in persistent juvenile obesity than in adult obesity and are an important cause of failure of treatment.

The prognosis in juvenile obesity, and probably also in adult obesity, depends largely on the intelligence of the patient.

Every effort should be made to treat obesity when it first occurs.

Research should be directed particularly towards the treatment of obesity in patients of low intelligence.

I am grateful to Dr. Alexander Kahan, of St. James's Hospital, on whose patients this investigation was done. I should like to thank Dr. J. C. Burkinshaw and Mr. M. P. Curwen for information and advice, Mr. F. A. Tubbs, Librarian of St. Thomas's Hospital and his staff and Miss M. E. Charlton, Records Officer of St. James's Hospital for their assistance, Miss E. Mason for drawing the diagrams and Mrs. J. Smith for untiring secretarial assistance.

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DIABETES INSIPIDUS FOLLOWING TUBERCULOUS MENINGITIS

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In tuberculous meningitis the site of the maximal infection and of the most dense exudate is the basal cisterns, particularly the cisterna chiasmatis and the cisterna ambiens. This exudate may lead to obstruction of the cerebrospinal fluid pathways, which can be readily demonstrated by pneumoencephalograms (Lorber, 1951). Calcification of this exudate occurs in a large proportion of children who recover from the disease and can be shown two or three years after the onset of the meningitis on radiographs of the skull (Lorber, 1952; Lorber, 1958). These lesions are in close proximity to the pituitary gland and the hypothalamic nuclei. They may lead to vascular thromboses and consequently to softening of the adjacent brain substance. Furthermore, the hypothalamic nuclei may suffer as a consequence of the variable degrees of hydrocephalus produced by the obstruction of the cerebrospinal fluid.

In view of these very common developments it would be reasonable to expect endocrine sequelae to result from a disturbance of the posterior pituitary-hypothalamic mechanism. Of the endocrine disorders originating in this area diabetes insipidus is one of the best recognized examples.

Nevertheless, although by now thousands of patients must have survived tuberculous meningitis, reports of diabetes insipidus occurring as a complication during or after this illness are very few indeed (Table 1) and none of the reports furnished adequate proof of a true diabetes insipidus. All the reported cases had polyuria and polydipsia, and it is possible that full proof of diabetes insipidus was established in some of them by appropriate endocrinological tests, but these were not published. This certainly applies to the patient of Hooft and van Winckel (1957) about whom Professor Hooft kindly supplied fuller details in a personal communication which fully established the diagnosis of true pitressin-sensitive diabetes insipidus. It is possible that the 11 cases briefly summarized in Table 1 are an incomplete list. The literature on tuberculous meningitis is so vast now that mention of some cases in papers not specifically dealing with endocrine sequelae or with follow-up studies may have escaped detection. The table does not include a few cases quoted by authors without details or quoting exact references. It is noteworthy that, with one exception (Acheson and Smith, 1958), none of the reported cases was in the British or American literature.

No case of diabetes insipidus has developed among 131 surviving children who were treated in the Children's Hospital, Sheffield, and who were followed for two to 10 years after their admission. We have, however, seen and investigated a child through the courtesy of Dr. J. S. Oldham, who referred him to us because of polyuria and polydipsia, and who was proved to have true diabetes insipidus.

Case History

R. was born on February 9, 1945, and was the oldest of three children. He weighed 7 lb. He contracted tuberculous meningitis in 1948 at the age of 3½ years and was treated with intramuscular and intrathecal streptomycin. The total duration of treatment was 75 days and during this time he received 40 intrathecal injections of 50 mg. each. Following this illness he was left with severe visual and hearing defects. He was almost blind in the left eye and had poor vision in his right eye. His left ear was almost deaf and his right ear was also affected. His mental development was normal and he attended ordinary schools, as no vacancy could be found for him in a school for partially-sighted children. His headmaster reported that in spite of his physical handicaps he successfully competed with his contemporaries in academic work and he would have been above the average but for his disabilities. According to the school records his height and weight were as follows:

Date	Age (yrs.)	Height (in.)	Weight (lb.)
4.10.51	6 8/12	42¼	43¼
23.11.53	8 9/12	47	51
1.6.56	11 4/12	48	56

In February, 1957, at the age of 12 years, he was struck on the head by a football. He was dizzy, but was not

TABLE 1

REPORTED CASES OF PRESUMED DIABETES INSIPIDUS FOLLOWING TUBERCULOUS MENINGITIS

Author	Number of Cases	Age (years)	Onset related to Meningitis	Other neurological Defects	Other endocrine Defects	Proof of Diabetes Insipidus	Comments
Asperger (1948) ..	1	Child	? During meningitis	Multiple	—	Clinical only	Doubtful case
Pinna (1953)	1	8	During meningitis	Died	—	Clinical and necropsy	
Conese, Colonna and La Pesa (1954) ..	1	25	Soon after recovery	No details	—	Polyuria and polydipsia urine S.G. 1,002-4	Not proven
Kissel and Arnould (1954)	1	24	11m. after recovery	+	—	Polyuria	Recovery after air encephalogram
Inglessi (1954)	1	14	3 yr. after recovery	—	Sexual infantilism	Pitressin-sensitive Polyuria and polydipsia	
Riser, Geraud, Ribaut, Gleizes, Rascol and Saint Marc (1955) ..	1	24	During treatment	—	Schizoid	Clinical	Complete recovery after 2½ yr.
Post (1955)	1	Child	After recovery	No details	—	No details	
Castel-Branco (1956) ..	2	7	During meningitis	—	—	Pitressin-sensitive	Recovery after 2 yr.
		6	3 m. after onset	—	—	Clinical	Good response to cortisone
Hooft and van Winckel (1957)	1	6	4 m. after recovery	—	—	Proved by water restriction test* Pitressin-sensitive	
Acheson and Smith (1958)	1	10	62 m. after onset	None	Atrophy of left testis (normal puberty)	Pitressin-sensitive Extreme polyuria (S.G. 1,000-6) and polydipsia	Doing well on pitressin tannate (S.G. 1,018-24)

* Personal communication.

rendered unconscious. During the following month he complained of headaches of increasing frequency and severity, but vomited only once before his admission to the Staincliffe General Hospital, Dewsbury, on March 6, 1957. On admission there he was found to have meningism and bilateral optic atrophy. The cerebrospinal fluid contained 106 white cells/ml. with 98% lymphocytes, protein 170 mg. %, chlorides 730 mg.%, and sugar 25 mg. %. Acid and alcohol fast bacilli were seen in the deposit and were repeatedly found in the cerebrospinal fluid for nine days after admission. In due course tubercle bacilli were grown on culture and were recovered from inoculated guinea-pigs. His urine was persistently acid, had a specific gravity of 1,012 on two occasions, contained a trace of albumin and there were approximately 20 leucocytes per high power field in the deposit. Acid-alcohol fast bacilli were detected in several specimens of urine up to the end of April, 1957, and tubercle bacilli were cultured and recovered from inoculated guinea-pigs. The organism was resistant to 10 μg. and sensitive both to 30 μg. of streptomycin per ml., and to 5 μg. of isoniazid per ml. A radiograph of the chest showed no lesion. A radiograph of the abdomen showed a dense calcified shadow at the level of the third lumbar vertebra, near the midline, but sometimes to the left and at another time to the right side, indicating that it was a calcified mesenteric lymph-node. A radiograph of the skull (Fig. 1) showed a dense crescentic calcification just below the posterior clinoid process of the sella at and slightly to the right of the midline.

The blood picture and blood urea were normal.

A diagnosis of a relapse of tuberculous meningitis was clinically, radiologically and bacteriologically established. An additional diagnosis of renal tuberculosis was made and this was confirmed later by an intravenous pyelogram (Fig. 2) which showed considerable right-sided hydronephrosis with a dilated and rigid right ureter. Cystoscopy was performed later and this showed inflammation around the right ureteric orifice. The orifice was depressed and was reminiscent of a 'golf hole ureter'. Catheterization of the left ureteric orifice was easy, but the catheter could not be passed into the right orifice. The urine from the left kidney gave a negative culture for tubercle bacilli.

Treatment. The treatment given was as follows: 1 g. of intramuscular streptomycin daily; 100 mg. of intra-

thecal streptomycin daily for 30 injections, followed by five injections in the next 11 days and followed again by daily injections for a further 16 days. (Total: eight weeks). Isoniazid was given orally in doses of 300 mg. daily from admission, and was started intrathecally in doses of 15 mg. daily a week later and continued for 18 injections. A second course of intrathecal isoniazid of 23 injections was given during the second month of treatment. In addition 5 mg. of hydrocortisone was given intrathecally daily from admission for 18 days and again during the third month from May 21 till June 10 for 21 injections. On stopping this 15 mg. of prednisolone was given by mouth daily for 17 days, 10 mg. daily for eight days and 5 mg. daily for three days.

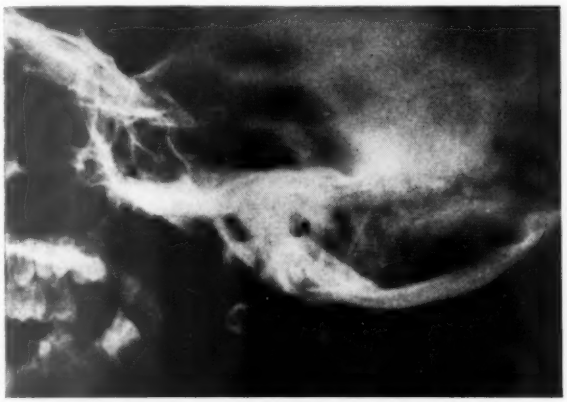

FIG. 1.—Radiograph of the skull showing calcification.

Progress. His condition slowly but steadily improved. He became more alert and lost his headaches. Occasional vomiting persisted for a few weeks but then ceased. The cerebrospinal fluid showed good improvement after the usual early fluctuations. At the end of May, 1957, it contained 11 white cells/c.mm., protein, 130 mg. % and sugar, 53 mg. %. By July 20, 1957, three and a half months after admission, the cerebrospinal fluid sugar had risen to 67 mg. % and he was thought to be well enough to go home for a holiday.

A single reading of the urinary specific gravity on July 11 had been only 1,002, and it was noted that he was drinking a great deal of water and had started to vomit water at night. He never vomited food. His urine was otherwise normal.

During his holiday at home his parents noticed increasing polydipsia and polyuria. His headaches returned and he now vomited frequently. He was readmitted to hospital on August 2, 1957, severely dehydrated. There was no deterioration in the neurological signs or in the cerebrospinal fluid, but he continued to vomit and developed a peripheral circulatory failure of such an extent that he required intravenous rehydration. During the next month he continued to drink large quantities of fluids averaging five to six pints daily and to pass even larger quantities of urine of the order of five to nine pints daily. The specific gravity was persistently very low but during a concentration test a single figure of 1,020 was obtained. At the same time the vomiting became incessant although findings in the cerebrospinal fluid remained fully satisfactory and there was no evidence of renal failure.

In view of these unfavourable developments he was transferred for further investigations to the Children's Hospital, Sheffield, on September 3, 1957. On admission his general condition was good. He was alert and interested, strikingly small for his age (12½ years) but not thin. His standing height was 49½ in. (126 cm.).

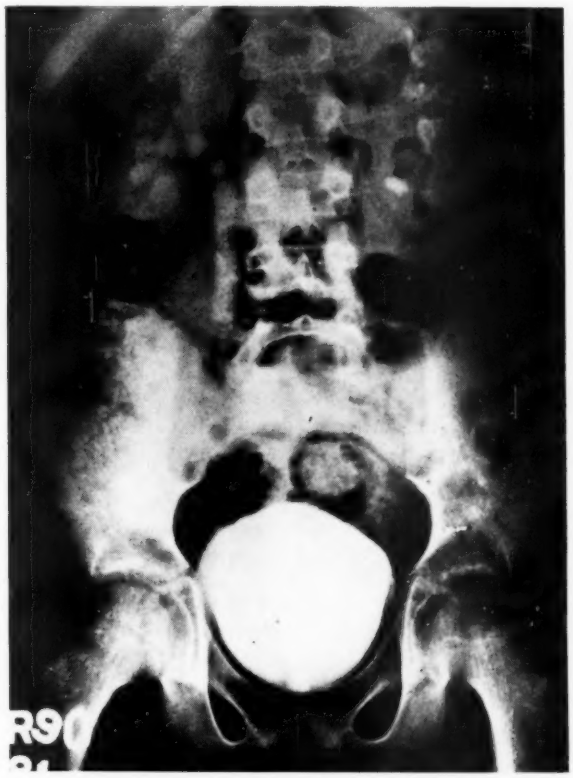

FIG. 2.—Intravenous pyelogram showing right-sided hydronephrosis.

His other anthropometric measurements were as follows: sitting height, 29½ in. (75 cm.); crown to umbilicus, 20¼ in. (51 cm.); umbilicus to sole, 29 in. (74 cm.); span, 51¾ in. (132 cm.). He weighed 60 lb. (27·5 kg.). Both his height and weight were below the third percentile for his age and corresponded to the 50 percentile of a boy of 7 years for height and 8 years for weight (Nelson, 1954). His penis and testicles were very small for his age and there were no secondary sexual characteristics.

The presence of bilateral optic atrophy and partial deafness was confirmed. Blood pressure was 120/80 mm. Hg. There was no meningism.

Investigations. The cerebrospinal fluid showed slight abnormalities consistent with recent tuberculous menin-

gitis (43 white cells, protein 55 mg.%; sugar 41 mg.%). His urine was normal chemically and microscopically and no tubercle bacilli were seen, cultured, or recovered from inoculation of guinea-pigs. The specific gravity, however, was persistently between 1,000 and 1,005. There was no evidence of renal failure.

His visual acuity was 3/60 on the right and there was light perception only on the left. The visual fields were not constricted. Electric audiometry showed a hearing loss of 30 to 40 decibels between frequencies of 128 and 2,048 on the right ear and 75 decibels on the left ear. The resting record of the electroencephalogram was normal but over-breathing produced an abnormally big build-up with dysrhythmic changes suggesting minimal, focal residual damage.

A radiograph of the skull confirmed the presence of the suprasellar calcification. An intravenous pyelogram showed a normal kidney outline on the left, but there was no visible secretion on the right. His bone age was between 7 and 8 years.

The polydipsia, polyuria and vomiting continued. He woke several times in the night to pass large quantities of urine, but he responded well to a trial of posterior pituitary snuff. As his polyuria could not be explained on a renal basis, the test recommended by Carter and Robbins (1947) (and modified from that of Hickey and Hare (1944)) was performed on September 10, 1957. (Fig. 3).

The test was performed as follows: fluids were withheld for eight hours preceding the test and then 20 ml. of water per kg. of body weight were given by mouth over a period of one hour. Thirty minutes after the period of hydration was begun, an indwelling catheter was inserted. Urine specimens were collected in 15-minute periods and the urine flow was calculated in ml. per minute. After two control periods with an adequate urine flow, a solution of 2·5% NaCl was given intravenously at the rate of 0·25 ml. per kg. per minute for 45 minutes.

Using this test on normal individuals or in those with psychogenic polyuria there is a marked reduction of urine flow beginning after 15 minutes. In cases of diabetes insipidus there is no response.

In the case of R. the urinary output during the first two 15-minute control periods was 5 ml. and 3 ml. per minute respectively. During the intravenous infusion of 2·5% saline there was no significant reduction in the rate of urinary flow whilst at the conclusion of the infusion and immediately after the rate rose to 8 ml. per minute. The specific gravity of the urine remained very low. The test showed conclusively that this was not a case of psychogenic or habit polyuria but true diabetes insipidus. He was then given an intravenous injection of 0·1 ml. of pitressin to find out whether the diabetes was of renal or pituitary origin. There was an immediate and gross reduction in the urinary output to 0·1 ml. per minute. The volume of this sample was too small for the estimation of the specific gravity, but that of the next sample was 1,012 (Fig. 3), showing that the diabetes insipidus was pitressin-sensitive and of pituitary-hypothalamic origin.

Treatment of the Diabetes Insipidus. Treatment was begun with pituitary snuff starting at first with one capsule in the evening and after two doses was continued with one capsule morning and evening. On this regime his fluid intake and urinary output fell by about one half and varied between two and three pints per 24 hours. The specific gravity of the urine frequently rose to 1,012. This was not considered to be sufficiently good control, especially as he still woke up several times in the night, and therefore his treatment was changed to intramuscular pitressin tannate. The dose was gradually increased from 0·3 ml. on alternate days to 0·6 ml. daily. On the latter dose his fluid intake varied between 23 and 31 oz., and his urinary output between 15½ to 20 oz. daily. The specific gravity of the urine rose to 1,020. He stopped vomiting.

He was discharged home on a maintenance dose of 0·6 ml. of pitressin tannate on alternate days.

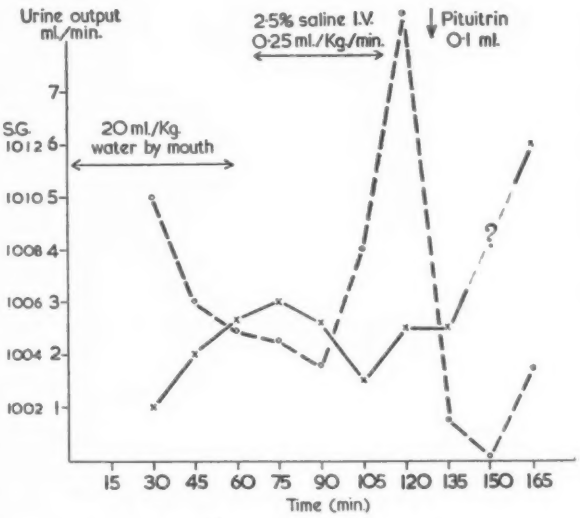

FIG. 3.—Result of Carter-Robbins test in a case of tuberculous meningitis followed by diabetes insipidus (10.9.57).

Family History. As it was apparent that this boy not only had diabetes insipidus but might be a pituitary dwarf with sexual infantilism, it was necessary to go into the family history with regard to stature and sexual development.

Both his parents were small. The father was 5 ft. 6½ in. tall (169 cm.) and his mother 4 ft. 11 in. (150 cm.). His sister who was two years younger was just taller than R. The two grandfathers were 5 ft. 5 in. (165 cm.) and 5 ft. 3 in. (160 cm.) and his grandmothers 5 ft. 4 in. (162 cm.) and 5 ft. (152 cm.) respectively. His maternal uncles and aunts were all of small build, but no measurements were available. The only available information regarding sexual development is that his mother's menarche was at 14 years and his maternal aunt's at 17 years.

Discussion

The diagnosis of diabetes insipidus of pituitary and hypothalamic origin has been established beyond doubt in our patient. He is now making good progress on pitressin treatment. It is not clear, however, whether the diabetes insipidus is a very late sequel of his first attack of meningitis which healed by meningeal calcification, or is the result of his second attack. In the earlier reported cases of diabetes insipidus the onset was either during the active phase of the meningitis or after recovery, but in none of them was it delayed by more than three years. Taking these features as guidance it seems likely that in our patient the second attack was the precipitating factor, although it is probable that the damage resulting from the first attack paved the way for the development of the disorder. That damage to the hypothalamic-pituitary mechanism did occur as a result of the first attack is undoubted, not only because of the presence of intracranial calcification immediately above the sella turcica, but more so because of the considerable retardation of the boy's growth and skeletal maturation, and by his apparent sexual infantilism. The last feature is not yet adequately proven as he is not quite 13 years old. Sexual infantilism and dwarfism was noted by Inglessi (1954) in a boy who was 14 years of age at the onset of the meningitis, and 17½ when the diabetes insipidus developed.

Another interesting feature of diabetes insipidus following tuberculous meningitis is that it is apparently capable of spontaneous recovery. Three of the reported cases recovered completely two to two and a half years after the onset, but in none of these was the diagnosis of a true diabetes insipidus adequately established.

Summary

This is a case of a boy who survived two attacks of tuberculous meningitis. The first attack occurred at the age of 3½ and he recovered with no deterioration in his good intelligence, but with grossly diminished vision and hearing. Subsequently his physical growth became very slow. At the age of 12 he had another attack of tuberculous meningitis. During the fifth month of treatment he developed the typical symptoms of diabetes insipidus. This diagnosis was established by salt and water loading tests. Treatment with pitressin led to satisfactory control of his polyuria and polydipsia. At the age of 13 he has shown no evidence of any secondary sexual characteristics.

The literature relating to diabetes insipidus following tuberculous meningitis is reviewed and its great rarity is noted.

I wish to thank Dr. J. S. Oldham for referring this patient to us, Professor C. Hooft and Dr. Honor V. Smith for details of similar cases under their care and Professor R. S. Illingworth for his criticism.

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DIABETES MELLITUS IN A CHILD SHOWING FEATURES OF REFSUM'S SYNDROME

BY

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This paper describes a diabetic child showing most of the features of a condition described by Refsum (Refsum, 1945, 1946*a* and 1946*b*, 1948, 1952; Refsum, Salomonsen and Skatvedt, 1949) under the name of heredopathia atactica polyneuritiformis. The malady is thought to be a recessive condition and is usually referred to as Refsum's syndrome. Only six other cases have so far been reported (Reese and Bareta, 1950; Clark and Critchley, 1951; Kjellson, 1953; Fleming, 1957; Olesen, 1957) and, as far as we are able to ascertain, no case has previously been described of this syndrome in association with diabetes mellitus. In view of the rarity of this association, we think that publication of this case is of interest.

Case Report

The patient, a girl, was first seen in the out-patient department in August, 1952, when she was 4½ years old. At that time she was the elder of two children, the other being a boy aged 7 months. Since then the mother has had a further child, a girl now aged 3 years. The patient had had anorexia for one month with weight loss, and also photophobia for a similar period. She had previously been quite well apart from an operation for intussusception at the age of 8 months. She was a thin girl, small in stature for her age. There was a left-sided concomitant squint and marked photophobia. Her urine was noted to contain sugar (2% Clinitest). She was admitted to the Sunderland Children's Hospital for further investigation, and particularly in order to determine whether she had diabetes mellitus. While in the ward she remained well and ate adequately. She had intermittent glycosuria, many specimens being free of sugar. During her stay in hospital she had marked photophobia and she was seen by Mr. A. Smith, consultant ophthalmic surgeon, Sunderland, who reported 'multiple epithelial erosions on both corneae'. It was thought that these could have been produced by sand when the child was playing on the beach one month previously. Her eyes were treated with 10% albucid drops and ung. atropine ½% twice daily. On this regimen the eyes became apparently normal within two weeks. A fasting blood sugar test was carried out, the result of which was 85 mg. per 100 ml.

She was discharged home but continued to lose weight and had persistent glycosuria; she was therefore readmitted to hospital in November, 1952. On this occasion her general condition was satisfactory, and her photophobia was not so obvious, but she had polyuria and persistent glycosuria. A blood sugar curve was typical of diabetes mellitus. The patient was given a 200 g. carbohydrate diet daily and soluble insulin was started in a dosage of two units twice daily. Following each injection, she became disorientated and drowsy. In view of this hypoglycaemic response an attempt was made to control her diabetes on diet alone but she continued to lose weight, and polyuria and polydipsia continued. Insulin was therefore recommenced and was now well tolerated; her diabetes appeared to be stabilized on a daily 200 g. carbohydrate diet with soluble insulin, seven units twice daily. She remained well on this regimen and, apart from a short admission to hospital for treatment of a left lower lobe pneumonia, she remained well though unusually small for her age until February, 1955.

In February, 1955, nearly three years after the start of her illness, the mother noted that the child was becoming increasingly deaf. She was seen by Mr. Rhys Evans, consultant ear, nose and throat surgeon, Sunderland, who reported that she had considerable, but not complete, bilateral hearing loss of perceptive type.

In April, 1956, nearly four years after the diabetes had been recognized, the mother noticed a progressively worsening tremor of both arms. Later titubation of the head began and in November, 1956, she began to be unsteady and to have difficulty in walking. She had to hold on to furniture to get round a room and her arms and legs became progressively weaker. She was seen by Dr. H. G. Miller, who diagnosed Refsum's syndrome and arranged admission to the Royal Victoria Infirmary, Newcastle-upon-Tyne.

On admission, aged 9 years, she was a pathetic figure, being totally deaf, dysarthric, small and underweight. She had an expressionless moon facies, and there was symmetrical wasting of the extremities of moderate degree. She had to be fed because of the severe tremor of her hands and preferred lying on pillows to sitting up. Her cardiovascular system was normal apart from a soft systolic murmur at the apex. Her skin was normal in texture and no rash or scaling was present. Abdominal palpation revealed enlargement of the liver about one and

a half inches below the costal margin. Her ears showed a circular depression in the centre of both drums, possibly old healed perforations. Her intelligence was not tested formally but was probably in the low average group for her age and there was no dementia. Her neurological condition was dominated by severe deafness, gross intention tremor, dysmetria and titubation made worse by exertion or emotional disturbance. She could not walk unaided. Her speech was grossly dysarthric, slow, scanning and slurred. There was symmetrical weakness of her whole face and bilateral ptosis with slight weakness of external rectus movement and occasional rotatory nystagmus. The pupils responded sluggishly to light and accommodation. The fundi showed atypical retinitis pigmentosa with right optic atrophy. The arms and legs were symmetrically wasted both proximally and distally and there was slight wasting of the hypothenar eminences, but no fasciculation was observed and there was no muscle tenderness. All four limbs were weak and flaccid. In the arms triceps and supinator jerks could just be elicited, whilst the biceps jerks and tendon reflexes in the legs were absent. The plantar responses were flexor; the abdominal reflexes were symmetrically brisk. Intention tremor, dysmetria and dysdiadochokinesia were severe in the upper limbs and the legs were also very ataxic. It was difficult to be sure of her cooperation in the appraisal of sensation. She could recognize and differentiate between touch and prick, though in view of the docile way in which she submitted to venesection, but not to certain other procedures, we regarded pain sensation as possibly diminished. The vibration sense was impaired in the lower limbs.

Investigations. The urine showed marked glycosuria without albumen or cells. Paper chromatography confirmed the presence of glucose with normal amino-acid excretion and no evidence of indican or other indoles in the urine. Twenty-four-hour urinary 17-ketosteroid excretion was 1·7 mg.

Blood examinations showed: haemoglobin, 16·3 g./100 ml.; W.B.C. 6,250/cu. mm.; the peripheral blood film appeared normal. The erythrocyte sedimentation rate was 3 mm. in one hour. Glucose tolerance curve was typically diabetic with a fasting blood sugar of 160 mg./100 ml. Serum calcium, 9·0 mg./100 ml.; diffusible, 4·1 mg./100 ml. (Greenberg, Larson and Tufts); serum protein: total, 6·6 g./100 ml.; albumen, 4·9 g./100 ml.; globulin, 1·7 g./100 ml. (by difference); plasma phosphate, 3·4 mg. phosphorus/100 ml.; plasma iron, 127 μg/100 ml.; serum cholesterol, 260 mg./100 ml.; plasma amino acid, 3·3 mg. α amino acid nitrogen/100 ml.; plasma bilirubin, total, 0·2 mg./100 ml.—directly reacting absent; zinc sulphate turbidity, 2 units; thymol turbidity, 3 units; thymol flocculation, 0; cephalin cholesterol, +; plasma alkaline phosphatase, 6·9 units (Jenner and Kay); plasma prothrombin, 80% of normal average (one-stage Quick technique). The Wassermann reaction was negative.

Radiographs of the skull, thoraco-lumbar spine and the hands and feet revealed no abnormality. An electrocardiogram showed abnormally flat and diphasic T waves; Q-T at upper limit of normal. Audiometry showed severe inner-ear deafness (70 decibels at 1,024 cycles per second). Vestibular function was normal as judged by caloric testing at 44 degree F. Perimetry was attempted, but the patient was not sufficiently cooperative to make the result worth while. Lumbar puncture (twice): normal pressure, 1 lymphocyte per cu. mm.; protein, on the first occasion, 120 mg./100 ml., on the second, 95 mg./100 ml.

On this admission the patient's diabetes was treated by giving a free diet and increasing her soluble insulin to 20 units twice a day. Several weeks later because of several hypoglycaemic attacks insulin was reduced to 15 units twice a day. At the present time the child is at home and is walking short distances with support.

The Family History. The paternal grandmother died of diabetes mellitus. There was no history of nervous disease in the two preceding generations. The parents and two siblings were clinically normal. The optic fundi, electrocardiograms and urine of the two siblings were also normal.

Discussion

The salient features of heredopathia atactica polyneuritiformis (Refsum, 1952) are (1) Atypical retinitis pigmentosa with hemeralopia and concentric constriction of visual fields. (2) A picture of chronic polyneuritis with progressive pareses of distal parts of limbs and decreased or absent reflexes. (3) Ataxia and other cerebellar signs. (4) Increased cerebrospinal fluid protein with normal cell count. (5) In some cases abnormal electrocardiographic changes have been noted, in others neurogenic hearing loss, pupillary abnormalities and skin changes resembling ichthyosis.

The condition of the child we have described resembles Refsum's syndrome although there are several unusual characteristics, chiefly, photophobia rather than night blindness and the presence of dysarthria. We have not demonstrated parental consanguinity or a hereditary tendency, but this does not exclude recessive inheritance; on the other hand the disease may be the result of a mutation.

Differential Diagnosis. The differential diagnosis from such diseases as toxoplasmosis and neurosyphilis presents no real difficulty.

Other heredo-familial degenerations, Friedreich's disease, cerebellar ataxias, familial spastic paraplegia, bear some resemblance to the case described but features such as nerve deafness and retinitis pigmentosa are not usually present in these conditions.

Peroneal muscular atrophy (Charcot-Marie-Tooth) and hypertrophic neuritis (Dejerine and Sottas) were deemed unlikely on account of the gross ataxia and dysarthria.

As far as metabolic disorders were concerned, there was no evidence of nutritional deficiency in this

child and there was no significant response to oral therapy with vitamin B complex. There was no abnormal amino aciduria; this would tend to exclude such conditions as hepatolenticular degeneration and the condition due to abnormal indole metabolism described by Baron, Dent, Harris, Hart and Jepson (1956).

In our patient the relationship between the diabetes mellitus and the degenerative condition of the central nervous system was obscure. The clinical picture was quite distinct from that of diabetic myelopathy (Garland and Taverner, 1953). Although the cerebrospinal fluid protein is elevated in both conditions, our patient's disease was insidiously progressive and quite unaffected by control of the diabetes. The family history suggests that the diabetes may have been independent.

There are many similarities between the degenerative conditions of the central nervous system in our patient and those of Friedreich's ataxia and other hereditary cerebellar ataxias and familial spastic paraplegia. It has been found that there is a higher incidence of diabetes in patients suffering from Friedreich's ataxia than in the comparable general population (Ashby and Tweedy, 1953). It now seems to be apparent that many of the heredo-degenerative diseases of the central nervous system are interrelated and that transitional cases occur. Refsum's syndrome may be another member of the hereditary ataxia group, along with Friedreich's ataxia, hereditary spastic paraplegia and peroneal muscular atrophy. It would therefore be of interest to know the incidence of diabetes mellitus in patients suffering from these degenerative conditions, and the incidence in members of affected families, as it might subsequently be possible, with adequate information, to demonstrate linkage or crossing-over between the gene or genes responsible for diabetes and those which produce the various hereditary ataxias.

Summary

A description is given of a child having many of the features of Refsum's syndrome together with diabetes mellitus.

The possible significance of the diabetes in this disease and other degenerative diseases of the central nervous system is briefly discussed.

We wish to thank Professor S. D. M. Court, Professor of Child Health, Durham University, and Dr. H. G. Miller, Department of Neurology and Neuro-surgery, Royal Victoria Infirmary, Newcastle-upon-Tyne, for their help and advice in this case and Dr. J. N. Walton for reading the manuscript.

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THE POST-NATAL WEIGHT LOSS OF BABIES BORN TO DIABETIC AND NON-DIABETIC WOMEN

BY

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The fact that babies of diabetic women are heavier as a group than those born at the same gestational age to non-diabetic women has been attributed in part to foetal oedema. Apart from their oedematous appearance, however, such infants are said to lose more weight in the immediate newborn period than babies of healthy women, and it has been concluded that this is the result of water loss. The object of the present paper is to review the evidence for a significant difference in post-natal weight loss between the babies of diabetic and non-diabetic mothers, and to present the results of a comparative study of post-natal changes in weight with special reference to the type of 'normal' babies used as controls.

Evidence for Weight Loss

Oedema. The greater weight of babies born to diabetic women has been ascribed by White (1952) to fat, visceral enlargement and fluid retention. She considered that the babies were often oedematous, and she believed that a diuresis was responsible for the abnormal weight loss. This opinion is reflected in such well-known textbooks as those of Baird (1950), Grulee and Eley (1952), Nelson (1954), Johnstone and Kellar (1955), Ellis (1956), Price (1956) and Dunlop, Davidson and Alstead (1958). According to White the oedema may be made to pit on pressure, but Gellis (1954) described it as non-pitting. This difference of opinion is of the greatest importance because if White is correct then the diagnosis of oedema cannot be doubted. If the oedema cannot be demonstrated by pitting, however, then the diagnosis cannot be confirmed without such direct evidence as may be obtained by measurement of the body water or by careful records of body weight and fluid balance. As White and Gellis have probably shared a number of their cases and have discussed them together (Gellis, White and Pfeffer, 1949) the wide divergence of opinion between two such acknowledged authorities indicates that doubt exists about the presence of pitting oedema.

Diuresis. Although a number of papers mention the occurrence of a diuresis in such babies, no real proof of its occurrence has been provided, and no record of a fluid balance study has been found. In a previous paper Farquhar (1956) measured the 24-hour urine volumes of infants born to diabetic and to non-diabetic women. The former babies received no fluid during the first 72 hours, but each passed on average about 60 ml. more urine during the first 48 hours than the control babies who were fed from the first day of life. During the third day there was little difference between the urine volumes of the two groups. The groups were small and they were not comparable with regard to maturity or the route of delivery, but the results strongly suggested that babies of diabetic women pass rather more urine initially than normal babies. The difference in volume, however, was so small that it could not be responsible for much difference in weight loss between the groups.

Weight Loss. The studies of White (1952) and Cardell (1953) on the post-natal weight loss of infants born to diabetic mothers are well known. Although White has the larger series her analysis of the subject is less satisfactory than is that of Cardell. Her description of the amount of weight lost does not prove that this was abnormal. She did not define what she meant by weight loss and she provided no information about the control group other than that the mothers were non-diabetic women who had been delivered at the same hospital over the same time interval. She compared only the average weight loss of the two groups and even this was in terms of absolute weight and made no allowance for the greater birth weight or different maturity of the babies of diabetic women. The babies in Cardell's study were grouped first according to birth weight. He was then able to show that infants of diabetic women in his series lost significantly more weight (expressed as a percentage of birth weight) than

'control babies' of comparable birth weight. He failed to define what he meant by weight loss, although he clearly did not mean the weight loss over a fixed time interval. He gave no idea of the variability of weight loss. His control group did not match his diabetic group with regard to either maturity or the route of delivery. Neither White nor Cardell provided any detail about the technique of weighing, the environmental conditions under which their diabetic and control series were nursed or how and when they were fed.

The Problem. Because the evidence in favour of foetal oedema is inconclusive, it was decided to examine in greater detail the post-natal weight loss of babies born to diabetic and non-diabetic women.

Most of the infants in the Edinburgh series, like those delivered in the hospitals from which both White and Cardell have published their papers, have been delivered by Caesarean section. It was decided to compare the weight loss of the diabetic group not only with that of infants delivered spontaneously to non-diabetic women but also with that of babies born by Caesarean section to non-diabetic women.

The diabetic group has been subdivided into two according to the feeding history. Between the years 1948 and 1951 most of these babies were fed early because of a fear that they might suffer from hypoglycaemia. When it became recognized that this was not harmful and that inhalation occurred rather easily on the first and second days, feeding was delayed in those infants born during the years 1952 to 1955.

Consideration has been given to the comparability of the groups and also to the environmental conditions in which the infants were nursed.

Composition of Groups

A. Diabetic Mothers. The infants of diabetic mothers delivered by Caesarean section during the years 1948-55 are divided into two groups, one of which (A1) consists of 31 babies who were fed within the first 24 hours. The second group (A2) consists of 29 infants who were unfed until aged 72 hours for the reasons already given.

B. Non-Diabetic Mothers. The infants of non-diabetic mothers are divided into two groups, one of which (B1) consists of 60 babies born by Caesarean section to women who had not been in labour before operation. The second group (B2) consists of 60 babies born spontaneously by the vertex *per vaginam*. These two groups are matched with one another for maternal age and parity.

The mothers of infants in group B1 were delivered in the years 1948-49 and 1953-54. They had Caesarean sections performed because of placenta praevia in almost half the cases, because of pregnancy toxaemia in less than one sixth, and because of disproportion or previous uterine scar in the remainder. So that they might be compared in ways other than those mentioned in this paper, as many as possible of the cases were of 36 to 38 weeks' gestation.

Infants in both groups B1 and B2 were fed during the first 24 hours. Those in group B1 usually received a bottle, whereas those in group B2 were put to the breast. Infants were excluded from groups B1 and B2 if they died later during the newborn period or if they had lost blood, were pyrexial or had any congenital malformation, infection or gastro-intestinal disorder which was considered by the clinician to have a possible influence upon the weight behaviour.

Comparability of Groups

Sex, maternal age, social class (husband's occupation), parity, birth weight and maturity have all been shown to be relevant to birth weight. It was not known to what extent these would also affect weight loss, but since they were readily available they were all taken into account. It was clearly impossible to match the groups according to all these criteria, but where possible maternal age and parity were selected for matching.* These are accepted as being of fundamental importance in birth weight studies. The other characteristics are also presented for comparison.

A. Diabetic Groups. Because these groups formed the consecutive halves of a naturally occurring series no previous matching according to the above criteria was possible. The two groups are evenly balanced for foetal sex, and there is no marked difference in parity. Group A2 contains rather more babies in higher social classes than group A1 (Fig. 1). There are rather more of the heavier babies in group A1 than in A2 because of the greater variability of birth weight in A1. There is also greater variation in the maturity of infants in group A1, so that the group contains relatively larger numbers of more mature infants than does group A2. The lower birth weight and lesser maturity of infants in group A2 reflects the adoption of a more rigid policy about Caesarean section at the 36th-37th week which was adopted about 1951.

* No relationship between the infants' weight loss and maternal age or parity was found by Naish and Edwards (1952) in their study of normal babies. It was decided, however, that for the better comparison of these abnormal and normal groups these two factors should be taken into account.

B. Non-Diabetic Groups. The spontaneous deliveries (B2) were matched with the non-diabetic Caesarean deliveries (B1) for maternal age and parity (Fig. 1). The two groups are evenly balanced for foetal sex. Rather more of the infants in group B1 are of social classes IV and V. There is no marked difference in birth weight, but the babies in group B1 are distinctly less mature.

DIABETIC AND NON-DIABETIC GROUPS. As a result of the comparative infrequency with which Caesarean section is carried out prematurely in the non-diabetic woman, the number of babies available for inclusion in this group was rather limited, and it was found impossible to match them for maternal age and parity with either diabetic group. Older women make up a greater proportion of the non-diabetic Caesarean group (B1) than in either A1 or A2, but there is less difference in parity. Birth weight is less scattered in the non-diabetic Caesarean group (B1) but the maturity is more evenly spread over the period 36 to 40 weeks than in the diabetic groups. It may be seen from Fig. 1 that the infants of group B2 are clearly more mature than those of group B1, which in turn are more mature than those of groups A2 and A1.

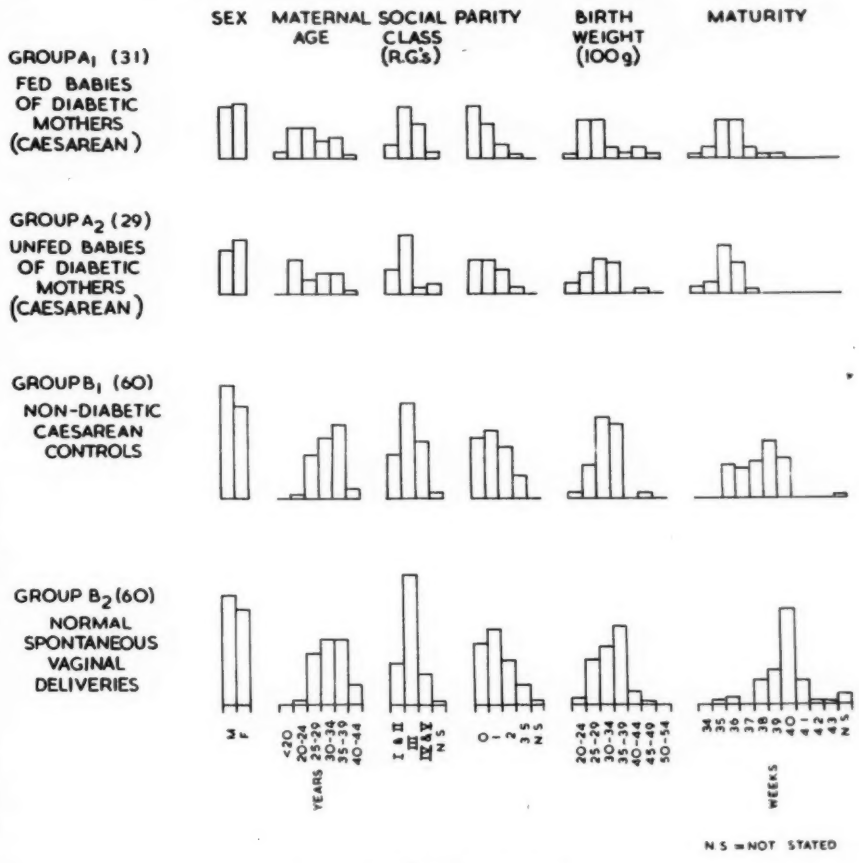

FIG. 1.—Comparison of the groups.

Environmental Conditions During the Period of Measurement

The babies of the diabetic groups were nursed nude in premature rooms at a temperature of 80°F. Those in group A1 were moved to the main nursery after 2-3 days, and those in group A2 graduated there on the fourth or fifth day. Only a small proportion of the babies in group B1 (non-diabetic Caesarean controls) was admitted to the premature room and then usually for no longer than 24 hours. Most of them were retained in the main nursery at an environmental temperature of 70°F. and normal humidity. The babies of group B2 (spontaneous deliveries) were admitted to the main nursery from the labour ward. In the nursery all infants wore a napkin and gown. They were rolled in a cotton sheet and blanket and covered by one blanket and a light cotton coverlet.

Method of Weighing

All the babies have been weighed naked on Avery scales which are tested regularly and which are accurate to ¼ oz. (7·1 g.). They are weighed on arrival from the labour room and at the same hour each morning thereafter. The majority of babies in groups A1, A2 and B1 were born in the forenoon by elective Caesarean section. The beginning of the second day on the weight chart therefore corresponded to an age of about 22 hours. Unfortunately in group B2 the actual age at the beginning of the second day on the chart ranged from eight to about 30 hours. The retrospective nature of the study made this unavoidable. Weights were graphed on the infant charts and the plotting of the points was found to be accurate to about ½ oz. (14·2 g.) when com-

pared with the written record. The weights of the infants in group B2 were recorded daily from birth. This applied also to the great majority of babies in group B1. In groups A1 and A2, however, the weight records during the first 48 hours were incomplete at times as some infants were nursed with the minimum of disturbance, and others were attached to experimental apparatus the efficiency of which would have been prejudiced by movement or disconnection.

Results

Criteria of Weight Changes. In defining what is meant by weight changes the features to be considered are the time interval over which the alteration occurs and the weight change in either absolute or relative terms. In this paper the relative weight loss each day is expressed as a percentage of birth weight.

Percentage Weight Loss in Relation to Birth Weight. The relationship between percentage weight loss and birth weight has been examined for several of the days after birth. No association was discovered on any of these days, and Fig. 2 illustrates this lack of

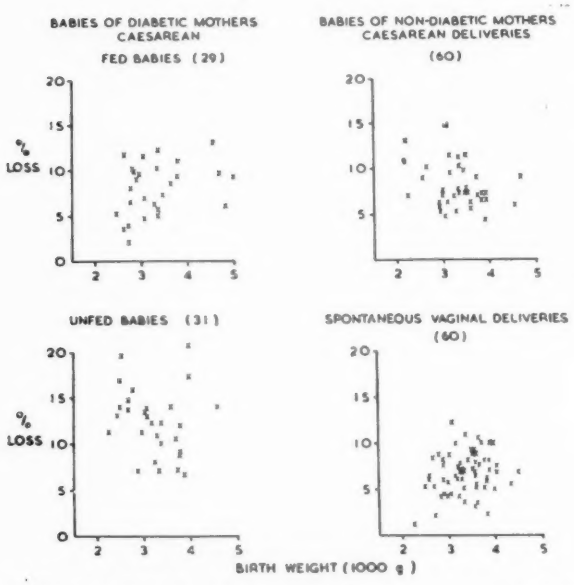

FIG. 2.—Post-natal weight loss on fourth day as a percentage of birth weight.

any relationship on the fourth day in all of the four groups. The variability of percentage weight loss changes with age. It is least at the third or fourth day after birth, and increases thereafter.

Method of Presentation. The individual weight record of each infant in the four groups has been studied and examples of the variability of individual

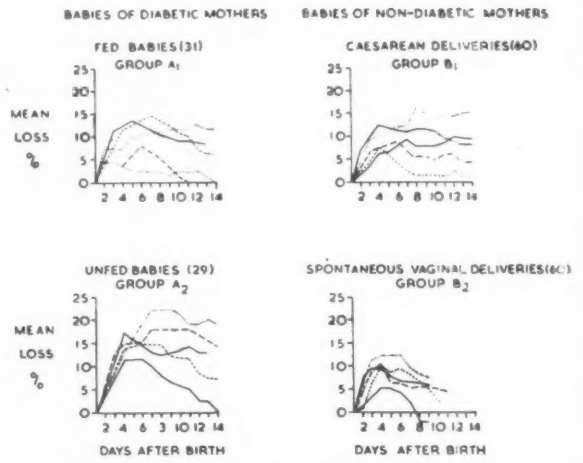

FIG. 3.—Examples of variation in post-natal weight loss in the four groups.

weight changes within each group are shown in Fig. 3. The main results, however, are presented as group averages with standard deviations (Fig. 4).

Group Differences in the Pattern of Weight Change (Fig. 4). (*a*) A significant difference in the pattern of weight change clearly exists between the two diabetic sub-groups. The unfed group (A2) loses more weight than the fed group (A1) and the rate of regain may be a little more rapid during the period up to 14 days.

(*b*) There were no significant differences in the trend of mean percentage weight changes between the fed diabetic Caesarean group (A1) and the non-diabetic Caesarean group (B1). The statistical significance of the differences between the means for each day after birth was assessed by Fisher's F test

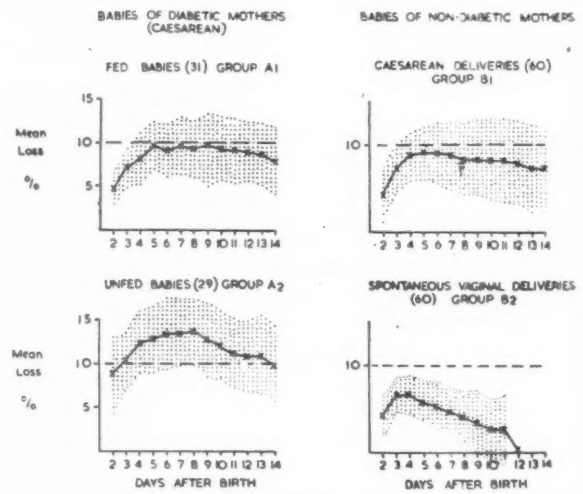

FIG. 4.—Group differences in the pattern of post-natal weight change. (Shading indicates ± one standard deviation about the mean.)

(Snedecor, 1956). In no case did the magnitude of the observed difference correspond with a probability of less than 1 in 5 ($p > \cdot 2$) of occurrence by chance in random sampling from a common population.

Although the percentage weight losses of the non-diabetic Caesarean group were slightly more variable than those of the fed diabetic group, there was no significant difference in their respective variability up to the 11th day as assessed by the F test.

(*c*) A significant difference in the pattern of weight change clearly exists between those of all the Caesarean groups (A1, A2 and B1) and that of the spontaneous group (B2). The latter loses less weight, and an earlier and more rapid regain of weight occurs.

Discussion

The newly born infant of the diabetic woman commonly has a puffy, sometimes even a bloated appearance which he loses during the first week of life. This puffiness has been attributed to oedema partly because it 'looks like oedema', partly because it changes so quickly, but mostly because pitting oedema has been demonstrated in some cases. The shedding of this fluid has been taken as the explanation of the apparent excessive post-natal weight loss. As we have stated already the babies were found by White (1952) to have pitting oedema, yet the same infants were found by Gellis (1954) to have non-pitting oedema. Neither author mentioned any exception. Oedema was accepted as the explanation of the appearance of such infants by the clinician in the Edinburgh series of over 100 cases. The baby charts appeared to show abnormal post-natal weight losses, but pitting oedema was rare and 'occult oedema' was assumed in the majority. In the second half of 1957 not one of 10 such babies showed convincing pitting oedema, although most of them were described as 'puffy' or 'flabby'. The largest of these weighed 5·0 kg. when delivered at the 36th week of gestation. He was stated by a midwife to have shown pitting oedema at birth, but when examined at three hours by one of us no evidence of it could be found. The greatest percentage weight loss of the 10 occurred in a baby who had shown no pitting oedema at birth and in whom even the characteristic puffy appearance was missing.

Direct measurement of the urine volume during the first 48 hours of life, however, showed that a group of babies born to diabetic mothers passed an average of only 60 ml. more urine than more mature infants born to non-diabetic mothers, and by the third day the urine volumes of the two groups were similar (Farquhar, 1956). Although this did in fact mean that the infants of the diabetic group passed three times as much urine on average as those of the non-diabetic group, such a difference would add comparatively little to the weight loss of infants in the diabetic group. Unless such babies lose relatively greater amounts of fluid from the skin, the lungs or the bowel, and no evidence of this has been reported, then some other explanation of their reported greater weight loss must be sought. In the first place the criteria and the consistency of weight loss should be examined.

Criteria and Consistency of Weight Loss. When it is remembered that the birth weights of infants born to diabetic women are often above average, it is clear that if their weight loss is to be compared in terms of absolute weight with that of infants born to non-diabetic women then the birth weights of the two groups must be given. This was not done by White (1952) who gave only the average absolute weight loss of the two groups. A proper comparison can be made only when the weight loss of each infant in the groups is expressed on each day as a percentage of birth weight. Although Cardell (1953) did express the weight losses of his diabetic and control groups in such relative terms he did not specify what he meant by weight loss. He probably did not take the amount of weight lost over a fixed time interval, such as from birth to the fourth day, and it may be assumed that he selected the maximum amount of weight lost irrespective of the time interval. A study of individual weight patterns in the present groups, however, has shown how difficult the selection of 'the point of maximum weight loss' may be. Quite commonly the regain of weight which follows the initial loss is interrupted by a further fall in weight which may be the result of inadequate feeding, infection or some unrecognized factor. The present paper shows the variability of individual weight patterns, but the means and standard deviations for each day and for each group have also been calculated and compared.

Comparability of Diabetic and Control Groups. The control cases recorded by both White and Cardell were born spontaneously and were usually some weeks more mature than their infants in the diabetic groups, most of which were delivered by Caesarean section. The possible influence of maternal age and parity was not considered in either. For these reasons their control cases were imperfect and it was decided that in the present investigation the diabetic groups would be compared with two groups of infants, one of which had been delivered spontaneously, and the other by Caesarean section, to non-diabetic mothers. Lack of knowledge about the exact age in hours of the present vaginal delivery group at the time of weighing probably makes very

little difference to the group's general pattern of weight loss. The retrospective study of Naish and Edwards (1952) suffers from the same defect. The average weight loss increases to 6·7% of birth weight by the fourth day, and from then steady regain of weight occurs. The pattern is similar to that described by Gregory (1871), Holmes (1896), Griffith and Gittings (1907) and Kotz and Kaufman (1939) and it is quite different from that of any of the Caesarean section groups.

If the percentage of birth weight lost were to increase as birth weight increases then group comparison of relative loss would be possible only if the groups were evenly matched with regard to birth weight. For this reason the relationship of birth weight to the percentage of birth weight lost was studied for each of the present groups, and no correlation whatsoever was found. This finding opposes that of Griffiths and Gittings (1907) but confirms that of Naish and Edwards (1952) with regard to vaginal deliveries, and extends the observation to infants delivered by Caesarean section either to diabetic or non-diabetic mothers.

Delayed Feeding. The influence of delayed feeding upon the weight of the newborn baby has been studied by Griffith and Gittings (1907) and by Rott (1910). They demonstrated that the less fluid an infant receives during the first three days the more weight he will lose. The giving or withholding of extra fluid before lactation was established was believed to have been responsible for either an increase or a decrease respectively in the weight loss of infants studied by Naish and Edwards (1952) and the time of the first feed was found by Salber and Bradshaw (1954) to influence subsequent weight behaviour. The withholding of fluids until after 72 hours in group A2 was expected to influence weight loss, and the likelihood of this was increased by the high environmental temperatures in which these babies were nursed. This group did in fact lose more weight than group A1, the infants of which received fluids on the first day and were moved to a cooler nursery after 24 hours. Infants which have been dehydrated by simple water deprivation will regain weight quickly when fluids are given and this may explain why group A2 regained weight a little more rapidly than group A1.

Foetal Maturity. Although the greater weight loss and slower weight regain of group B1 when compared with group B2 is associated with the lesser maturity of group B1, the slightly greater maturity of group B1 when compared with group A2 is not associated with a similar difference in group pattern of weight loss. The small immature baby is said by Smith (1951) to lose a greater percentage of its birth weight than the mature infant, because the less mature the baby and the lower his birth weight the longer will feeding be deferred. The present study strongly suggests that deferred feeding and possibly environmental temperature exert a considerable influence on weight loss. There is no clear indication that differences in maturity alone explain the wide differences between the two non-diabetic groups, but if there is an association between maturity and the pattern of weight loss in the non-diabetic groups then this clearly does not extend to the diabetic groups.

Route of Delivery. The post-natal weight loss of infants delivered either spontaneously or by Caesarean section to non-diabetic women has been studied by Furuhjelm (1954). He subdivided his Caesarean section group into those women who had been in labour before operation and those who had not. When he compared his three groups he found that the mean weight loss of all three was equal by the third day, when it constituted about 7·2% of birth weight. This corresponds closely to the behaviour of the two non-diabetic groups in the present paper. After the third day Furuhjelm's vaginal deliveries no longer lost weight, but both Caesarean section groups continued to lose weight for two more days. The group of infants who had been born by Caesarean section to labouring women then began to gain weight parallel to the vaginal group. The group of infants who had been born by Caesarean section to non-labouring women, however, gained weight much more slowly. This also corresponds to the behaviour of the two closely matched non-diabetic groups in the present paper.

Conclusion

Had the present study been concerned only with a comparison of the post-natal weight loss of babies born by Caesarean section to diabetic women and those delivered spontaneously to non-diabetic women, then agreement would have been achieved with White and with Cardell. The conclusion that the greater weight loss of the diabetic group was the result of shedding oedema would probably have been reached. The inclusion of a non-diabetic Caesarean section group and the effort made to match this with the vaginal group and to consider the other factors previously mentioned have altered the picture completely. No evidence has been found to confirm the belief that infants born by Caesarean section to comparable groups of diabetic and non-diabetic mothers differ significantly in their post-natal weight patterns. It cannot be said therefore that the exces-

sive weight loss of infants born to diabetic women is evidence of their having been oedematous.

No explanation is offered for the striking difference in post-natal weight between babies delivered by Caesarean section to non-labouring women and those delivered after normal labour. It is true that lactation is established more slowly in the woman delivered by Caesarean section, and during the waiting period complementary feeds may be kept small in order that the infant's hunger might act as a stimulus to the breast.

The process of labour was considered by Furuhjelm to be responsible for the differences in weight pattern between Caesarean and spontaneous groups, but the underlying condition for which Caesarean section is performed may be responsible. Furuhjelm failed to specify why the Caesarean sections were carried out on his patients, but if this were the explanation then, in the present study, diabetes mellitus would appear to have no greater influence on the post-natal weight of the foetus than placenta praevia, disproportion or previous uterine scar, which were the principal reasons for section in the control Caesarean group.

When ligature of the cord is delayed until the placenta is expelled the infant received considerably more placental blood. According to Zweifel (1878) such babies lose less weight post-natally than those whose cords were cut immediately after delivery. The cord is of course likely to be clamped more rapidly after delivery by Caesarean section than by the vagina, but Zweifel compared absolute weight losses, and his comparisons may not be valid.

Further studies will be required to explain this difference in weight behaviour, and in these the reason for Caesarean section, the nature of the labour, the time allowed to elapse before the cord is clamped, the maturity of the child and the details of feeding should be examined with greater care than has been possible in a retrospective study.

Summary

The abnormal heaviness of infants born to diabetic women has been ascribed in part to oedema.

The evidence in favour of the claims that because of this such infants lose more weight than normal babies in the post-natal period has been reviewed. Because of differences in the criteria of weight loss and in the management of the newborn, and because of the faulty construction of control groups, this evidence has been found inconclusive.

The weight loss of babies delivered by Caesarean section to diabetic women has been compared closely with that of babies similarly delivered to non-diabetic women and with babies born spontaneously to non-diabetic women.

When infants of diabetic women are subjected to prolonged fluid deprivation they lose more weight than when fluids are given early, and also lose more weight than infants of non-diabetic women by whichever route these have been delivered.

Infants of diabetic and non-diabetic women delivered by Caesarean section lose similar amounts of weight when nursed under similar conditions.

Infants delivered by Caesarean section to diabetic or non-diabetic women lose more weight over a longer period than infants delivered spontaneously to non-diabetic women. They also regain weight more slowly.

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JAUNDICE AND INFANTILE DIARRHOEA

BY

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Although it is recognized that infantile diarrhoea may sometimes be complicated by jaundice, the pathogenesis of this jaundice has not been fully elucidated. The only detailed account of the hepatic lesions in infantile diarrhoea is that of Wainwright (1950), who described in 11 of his 16 cases a form of 'hepatitis' characterized by periportal parenchymal necrosis, infiltration by polymorphonuclear leucocytes and mononuclear cells, proliferation of small bile ducts, inconstant fibrosis, periportal fatty change, distension of bile canaliculi in the centres of the lobules and congestion accompanied by varying degrees of centrilobular necrosis. In his remaining four cases there was centrilobular bile retention only. Wainwright noted a resemblance to experimental allyl formate poisoning and considered the hepatitis to be due to toxic parenchymal damage. Holland and O'Connor (1949) also attributed liver damage in infantile diarrhoea to hypothetical toxins, whilst Schlesinger, Payne and Burnard (1949) invoked nutritional deficiency.

The 13 cases which form the basis of this report came to necropsy in the Bernhard Baron Institute of the London Hospital in the years 1934 to 1954. They appear essentially similar to those described by Wainwright, although a different interpretation will be placed upon the pathogenesis of the hepatic lesions.

Description of Cases

In 9 of the 13 cases jaundice was noted during life or at necropsy. The remaining four cases were encountered unexpectedly when histological preparations were examined from 50 'control' cases of infantile diarrhoea without recorded jaundice which had come to necropsy in the years 1929 to 1956. Since in the same period there were many necropsies upon similar cases in which the liver was not examined microscopically, the true incidence of the lesions to be described could not be assessed. The hepatic lesions in the four cases without recorded jaundice were essentially similar, both qualitatively and quantitatively, to those found in cases with overt jaundice. The main features of all 13 cases are summarized in the Table.

Aetiology. The stools were examined bacteriologically in eight cases, no pathogenic organisms being found. In only the most recent case however was special search made for pathogenic strains of *Esch. coli*. The possibility of infection from a single source or of cross infection arose only in Cases 1, 2 and 8, all three of whom were in the same ward of the hospital at the same time. Two of these (Cases 1 and 8) developed both diarrhoea and jaundice whilst in hospital, having been admitted for other conditions. Case 2 was admitted with diarrhoea, jaundice appearing later. At this time there was in the same ward a child of 5 years with clinically typical virus hepatitis.

Clinical Features. It has already been noted that in four cases jaundice was not recorded during life or at necropsy. In a fifth it was present at necropsy although there was no mention of it in the clinical notes. In these five cases the duration of diarrhoea was from eight to 22 days, and in the remaining cases it was from nine to 28 days. In all but one of this latter group diarrhoea preceded jaundice by a period of seven to 16 days. In Case 12 there was vomiting for two days before jaundice was noted, but diarrhoea did not commence for another 10 days. The duration of jaundice was short (one to four days) in five cases. In the remaining three it was nine, 18 and 37 days respectively. It is clear however, from the presence of hepatic lesions without recorded jaundice and from lack of correlation between the duration of jaundice and the apparent age of the lesions as judged histologically (see Table), that jaundice was an unreliable indication of hepatic involvement in this series. The available clinical and laboratory data gave no clear indication of the nature of the jaundice, although an obstructive element was suggested in some cases. Death was not definitely attributable to hepatic failure in any case.

TABLE

CLINICAL AND PATHOLOGICAL FINDINGS IN 13 CASES OF INFANTILE DIARRHOEA WITH JAUNDICE

Case No.	Sex, Age (mths.)	Duration (Days) of Diarrhoea	Duration (Days) of Jaundice	Bile Thrombi	Proliferation of Bile Ducts	Infiltrate in Portal Tracts	Fibrosis	Fatty Change	Siderosis
1	F 5	9	2	Scanty	Slight	Scanty polymorphs	Absent	Marked	Slight
2	F 5	13	4	Scanty	Moderate	Many polymorphs	Slight	Marked	Absent
3	M 5	17	1	Scanty	Marked	Moderate polymorphs	Slight	Very marked	Absent
4	M 2½	8	Absent	Many	Slight	Slight polymorphs	Absent	Slight	Slight
5	M 4½	17	Absent	Scanty	Slight	Scanty polymorphs	Absent	Marked	Absent
6	M 8	13	Absent	Moderate	Moderate	Moderate polymorphs and lymphocytes	Slight	Marked	Absent
7	M 4½	10	P.M. only	Many	Moderate	Moderate polymorphs and lymphocytes	Slight	Moderate	Absent
8	F 8	28	18	Moderate	Probably slight	Scanty mononuclears	Moderate	Slight	Moderate
9	F 2	9	2	Many	Slight	Scanty mononuclears	Moderate	Slight	Moderate
10	F 2½	19	9	Moderate	Doubtful	Scanty mononuclears	Marked	Moderate	Slight
11	M 4	13	1	Many	Slight	Absent	Slight	Absent	Moderate
12	F 2½	27	37	Many	Absent	Absent	Absent	Absent	Marked
13	F 9	22	Absent	Moderate	Absent	Absent	Absent	Absent	Slight

Pathology. Focal ulceration of the gastro-intestinal tract was noted at necropsy in one case only. Histologically the stomach and intestines in the remainder showed only a mild or moderate non-specific acute inflammatory process, sometimes with marked oedema. Changes in organs other than the alimentary tract and liver were incidental or unimportant.

The hepatic lesions could be divided histologically into those (Cases 1 to 10, hereafter called Group I) in which there was, in addition to bile retention within the lobules, evidence of an inflammatory process in and around the portal tracts; and those (Cases 11 to 13, Group II) in which the appearances were those of obstructive jaundice without evidence of infection. This division (which is similar to that made by Wainwright, 1950) may not however be an absolute one, for, as the Table shows, there were borderline lesions (particularly in Case 4) in which biliary obstruction was marked and portal inflammation only slight.

GROUP I. In all 10 cases distended bile canaliculi at the centres of the lobules suggested obstruction to the flow of bile, slight in Cases 1, 2, 3 and 5, moderate or well-marked in the remainder (Fig. 1). In the first seven cases there was a polymorphonuclear leucocytic infiltration of the portal tracts, some of these cells being within the lumina of small bile ducts but the majority lying in the portal connective tissue or at the extreme periphery of the lobules (Fig. 2). A slight degree of periportal fibrosis was present in Cases 2 and 3 and also in Cases 6 and 7, where the presence of lymphocytes as well as polymorphonuclear leucocytes provided additional evidence of a relatively subacute inflammatory process. In Cases 8, 9 and 10 fibrosis was more pronounced, the inflammatory cell infiltrate was mild and polymorphonuclear leucocytes were virtually absent. Proliferation of small bile ducts was seen in all the more acute cases (Figs. 2 and 3), mitotic figures being usually present. Where periportal fibrosis was at all marked however it was difficult to distinguish such newly formed ducts from parenchymal trabeculae caught up in the fibrous tissue. Fatty change was present in all 10 cases, although in very varying degree. Except in the liver with most fat (Case 3) it was essentially periportal in distribution. There were no necrotic cells still *in situ* in the first nine cases. It was apparent however that, as a result of periportal inflammation, some cells had been lost from the extreme periphery of the lobules, and the presence of parenchymal mitotic figures in three cases was additional evidence of this. In Case 10 there was marked sinusoidal congestion at the centres of the lobules, and there appeared to be some loss of parenchymal cells associated with this. There was however no condensation of reticulin in the central zones, and it is probable that much of the apparent cell loss was a post-mortem artefact. Finally, slight to moderate haemosiderosis was found in five of the 10 cases, both parenchymal cells and reticulo-endothelial cells containing pigment.

GROUP II. In Cases 11, 12 and 13 inflammatory changes were absent and the most striking abnormality in the liver was moderate or pronounced

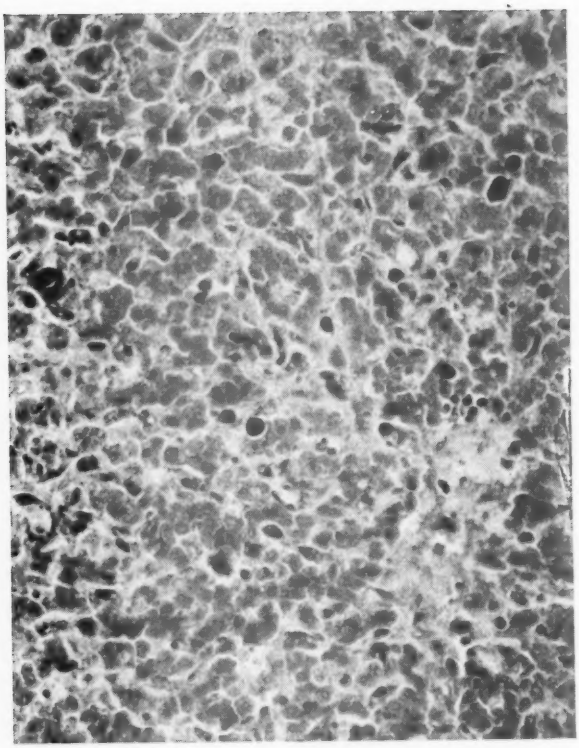

FIG. 1.—Case 4. A central vein is shown near bottom right-hand corner. There are several darkly stained bile thrombi, the majority in the centrilobular region. Haematoxylin and eosin. ×185.

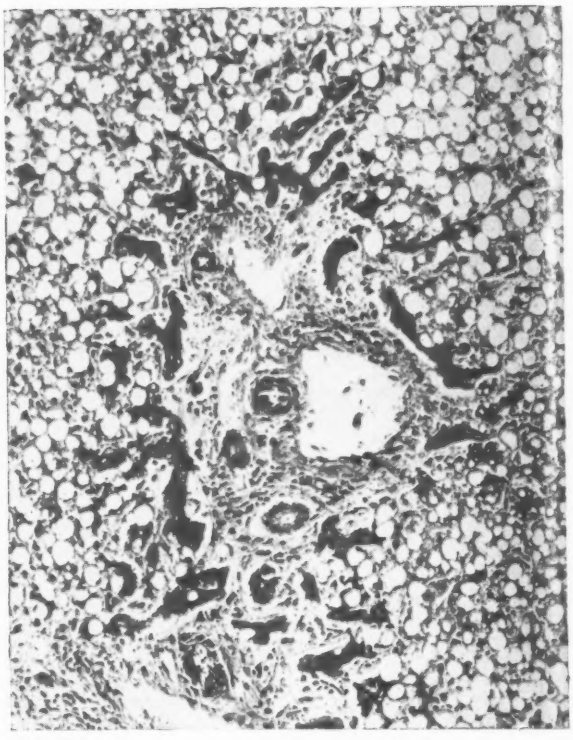

FIG. 3.—Case 6. Proliferation of small bile ducts around a portal tract and severe fatty change. Phosphotungstic acid-haematoxylin. ×120.

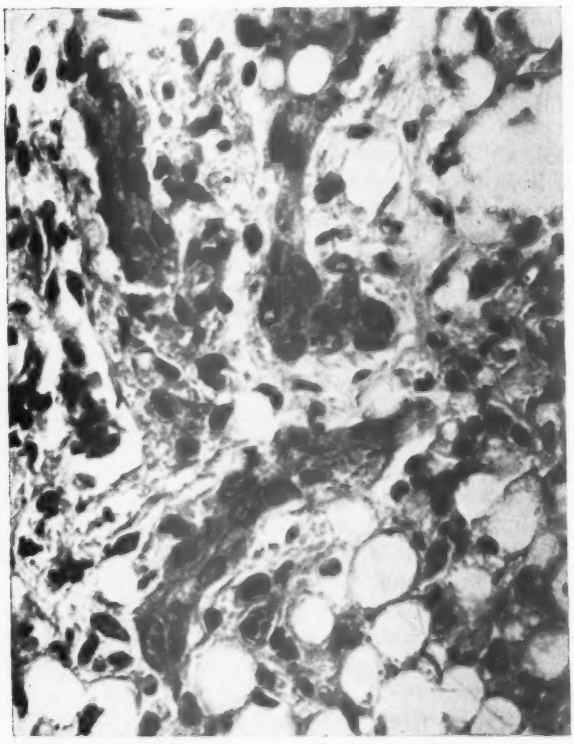

FIG. 2.—Case 2. Periportal fatty change, proliferation of small bile ducts and infiltration by polymorphonuclear neutrophils. Haematoxylin and eosin. ×490.

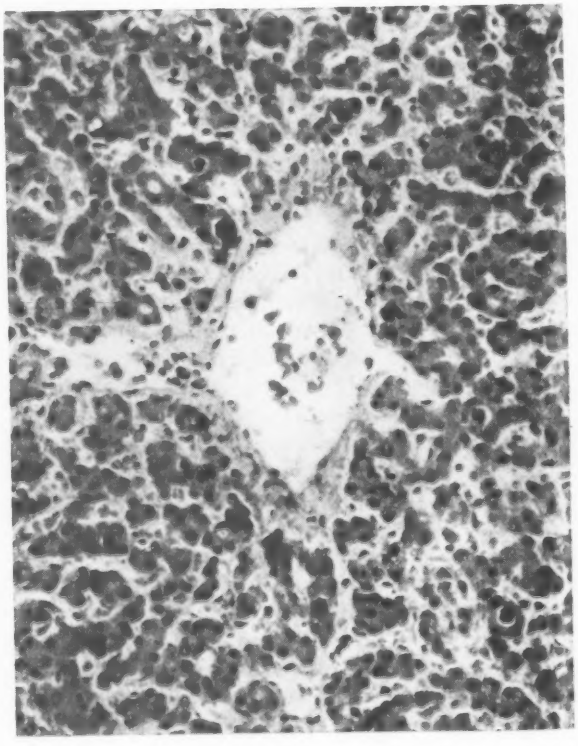

FIG. 4.—Case 11. Bile thrombi in central zone of lobule. Periodic acid-Schiff. ×185.

intralobular bile retention (Fig. 4). In Case 11 there was also slight proliferation of small bile ducts such as occurs in obstructive jaundice without accompanying inflammation, and the very slight degree of periportal fibrosis was no more than might be expected to accompany such bile duct proliferation. In Case 12 a few eosinophilic necrotic cells were present, but the appearances did not otherwise suggest virus hepatitis. Haemosiderosis was present in all three cases and occasional focal parenchymal necroses in the third.

Discussion

The pathogenesis of the hepatic lesions in these cases must be inferred very largely from the histological findings. Certain deductions of negative value may first be made. Thus although three cases (Cases 8, 9 and 11) had received blood transfusions, the microscopical features (many bile thrombi in all three, moderate periportal fibrosis in two and bile duct proliferation in the third) could hardly be attributed to haemolysis. Next, the only resemblance to neonatal hepatitis as described by Dible, Hunt, Pugh, Steingold and Wood (1954) was the presence of haemosiderosis in seven cases. A similar degree of iron pigmentation was noted in several cases of infantile diarrhoea without the hepatic lesions described above, and it was considered therefore to be a relatively non-specific finding. Nor was the picture that of virus hepatitis as seen in older subjects, the infiltration by polymorphonuclear leucocytes being particularly against this diagnosis.

Wainwright (1950) considered the essential hepatic lesion in most of his cases to be periportal parenchymal necrosis, the other changes being secondary. In all the lesions described here periportal necrosis was minimal, being readily accounted for by the inflammatory process in and around the portal tracts. It was this portal and periportal inflammation which, together perhaps with extra-hepatic biliary obstruction, appeared to be the essential hepatic abnormality in the first 10 cases in this series. Localization of the inflammation to the portal tracts might have been due to haematogenous infection, but the available evidence favoured rather an initial infection of the biliary tract, an ascending cholangitis. Thus inflammatory cells were sometimes present within the lumina of the smallest bile ducts and these same ducts showed unequivocal evidence of proliferation. Bile retention was usually in excess of what might have been expected from the amount of parenchymal damage present, and was therefore probably the result of biliary obstruction. The inflammation in and around the portal tracts probably contributed to this obstruction, but poor correlation between the intensity of the inflammation and of the bile retention suggested that the larger bile ducts may sometimes have been partly occluded. Extra-hepatic biliary obstruction was not found at necropsy in any case in this series or in that of Wainwright, and this author, whilst noting the resemblance of his lesions to cholangitis, considered the absence of demonstrable obstruction to be clear evidence that this was not their true nature. There are two objections to this conclusion. First it is doubtful whether the routine examination of the bile ducts performed at necropsy is adequate to exclude obstruction due to inflammatory swelling in the infant especially when, as the clinical evidence usually suggested in this series, the obstruction is incomplete. Secondly, whilst ascending cholangitis is very frequently associated with obstruction in adults, it would be wrong to assume that it cannot occur in the absence of obstruction in infants. Absence of inflammation in the extra-hepatic ducts would be important evidence against a non-obstructive ascending cholangitis. Wainwright failed to find such inflammation, but it is not clear how often the large bile ducts were examined in his cases. Unfortunately no sections of the extra-hepatic ducts were taken in the present series. In one section of the gall-bladder (Case 9) there was definite evidence of mild inflammation.

It is considered therefore that the hepatic lesion in the first 10 cases of this series was essentially a cholangitis associated with bile retention which may have been due in part to inflammatory obstruction of the extra-hepatic bile ducts, a true catarrhal jaundice in fact. Case 4, in which bile thrombi were numerous and inflammatory infiltration was slight, possibly bridged the gap between this group and the remaining three cases in the series (Group II) in which there was obstruction without evidence of intra-hepatic infection. Perhaps in these three cases the cholangitis had failed to reach the intra-hepatic ducts. On the other hand Case 12 was unusual clinically in that jaundice preceded the diarrhoea, and it may be therefore that a different pathological process was in operation. Virus hepatitis could not be ruled out with certainty in this case.

No pathogenic organisms were isolated in these cases and the nature of the infecting agent remained obscure. Despite a history of contact with virus hepatitis in three cases the histological evidence favoured a bacterial rather than a viral infection. On epidemiological grounds it seemed possible that at least two of these same three cases had been

infected from a single source. But it would be wrong to assume from this that there exist distinct icterogenic strains among the causative organisms of infantile diarrhoea. Cholangitis is not so uncommon a complication of this condition that it would be highly unlikely to occur in three successive cases by chance. Further bacteriological and epidemiological evidence is necessary to settle this point.

Summary

Nine fatal cases of infantile diarrhoea with jaundice and four cases without recorded jaundice but with identical hepatic lesions are described.

In 10 of these cases evidence of bile retention was associated with an inflammatory process in the portal tracts which was considered to be a cholangitis. In the remaining three cases there was bile retention without inflammation.

It is suggested that all cases may represent an ascending infection of the bile ducts, sometimes stopping short of the smallest ducts and associated with varying degrees of biliary obstruction. A bacterial rather than a viral infection is favoured but the causative organism was not identified.

I wish to thank Professor D. S. Russell for her helpful criticism and Dr. K. H. Tallerman and Dr. R. H. Dobbs for permission to include cases under their care.

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CONGENITAL SPHEROCYTOSIS IN INFANCY

BY

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Neonatal jaundice and anaemia of infancy are both common diagnostic problems. Very rarely, both these symptoms may be due to congenital spherocytosis and, unless there is a known family history of the condition, their diagnosis may be very difficult. Difficulties in diagnosis were encountered in identical twins, whose case is reported here, and whose neonatal jaundice and subsequent anaemia were thought at first to be associated with prematurity. The unusual course of the anaemia (Fig. 1) subsequently revealed the correct diagnosis even in the absence of other affected members of the family.

The clinical features of these two cases, together with a further 41 previously reported cases occurring in the first year of life, are summarized later in Table 1. This table is analyzed in order to determine the characteristic features of congenital spherocytosis in infancy, and the management of these patients is discussed.

Case History

Female twins were born on March 22, 1956, to a multiparous woman after a 36-week normal pregnancy. Both were vertex presentations and the first weighed 4 lb. 5 oz. (1,970 g.) and the second weighed 3 lb. 12 oz.

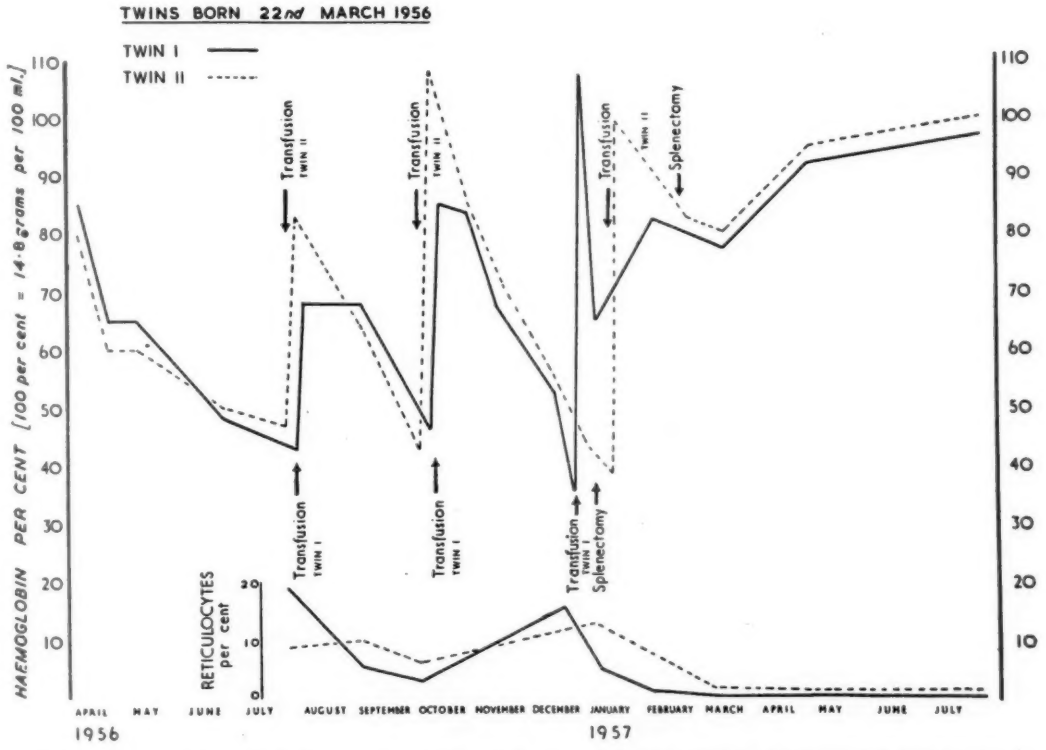

FIG. 1.—Course of anaemia in identical twins suffering from congenital spherocytosis, and progress after splenectomy.

(1,720 g.). Dissection of the placenta and membranes showed that they were monochorionic. The twins appeared identical except that there was webbing of the second and third toes on the left foot in Twin 1 only. The blood groups of both are Group O, Rh phenotype C C D ee (probable genotype CDe/CDe), M N, S+ve, P+ve, Lu−ve, K−ve, Le^a+ve, Le^b−ve, Fy^a−ve.

On March 26, both twins were noticed to be severely jaundiced and this continued until April 13. On April 5, the children appeared pale and the haemoglobin of Twin 1 was 85% (12·5 g. per 100 ml.) and of Twin 2 80% (11·8 g. per 100 ml.). By April 11 the haemoglobin had fallen to 70% (10·4 g. per 100 ml.) in both twins and on April 19 was 65% (9·6 g. per 100 ml.) and 60% (8·9 g. per 100 ml.) respectively. The twins were considered to have anaemia of prematurity associated with multiple birth. They were given ferrous sulphate from April 21, at first in doses of ¼ gr. (16 mg.) twice daily and from May 2 ½ gr. (32 mg.) was given twice daily. By June 19, Twin 1's haemoglobin had fallen to 48% (7·1 g. per 100 ml.) and Twin 2's to 50% (7·4 g. per 100 ml.) and both twins had palpable spleens. They were then given 3½ ml. of Imferon (Bengers) intramuscularly during the next month. On July 24, the twins' haemoglobin levels were 45% (6·7 g. per 100 ml.) and 42% (6·2 g. per 100 ml.) respectively.

The twins were admitted to hospital from July 24 until August 4. Investigations on Twin 1, who weighed 10 lb. 3 oz. (4,660 g.), showed haemoglobin, 43% (6·4 g. per 100 ml.); packed cell volume, 19·5%; mean corpuscular haemoglobin concentration, 32%; mean cell diameter (halometer) 6·8 microns; the red blood cells showed marked anisocytosis, poikilocytosis and polychromasia; reticulocytes, 19%; and normoblasts, 10 per 100 nucleated cells. The urine contained no bile salts and no excess urobilinogen. Two intramuscular injections of 1 ml. each of Imferon were given and on August 1 a blood transfusion of 160 ml. of whole blood. The haemoglobin on August 2 was 68% (10·1 g. per 100 ml.).

Investigations on Twin 2, who weighed 10 lb. 1 oz. (4,600 g.), showed haemoglobin, 47% (7 g. per 100 ml.); packed cell volume, 18%; mean corpuscular haemoglobin concentration, 34·4%; the red blood cells showed marked anisocytosis, poikilocytosis and polychromasia; reticulocytes, 9%; normoblasts, 10 per 100 nucleated cells; in a red cell fragility test haemolysis began at 0·48% saline and was complete at 0·32% saline; serum bilirubin was 0·5 mg. per 100 ml. The urine contained no bile salts and no excess urobilinogen. Twin 2 was given two injections of 1 ml. of Imferon and on August 1 a transfusion of 160 ml. of whole blood. On August 2, her haemoglobin was 83% (12·3 g. per 100 ml.).

On leaving hospital both twins were given ferrous sulphate gr. 1 (65 mg.) twice daily, but their spleens continued to be palpable and their haemoglobin fell progressively. They were re-admitted from October 3 to October 12. The haemoglobin level of Twin 1 was 45% (6·7 g. per 100 ml.); the red blood cells (2,530,000 per c.mm.) showed marked anisocytosis, slight poikilocytosis, slight polychromasia, some appeared macrocytic and there were a few spherocytes; the colour index was 0·88; packed cell volume, 21%; mean corpuscular haemoglobin concentration, 31%; reticulocytes, 3·1%; normoblasts, 1 per 100 nucleated cells; the direct Coombs test was negative; serum bilirubin, 1·6 mg. per 100 ml. The urine contained no excess urobilinogen; the stools contained no occult blood and the fat content was normal. On October 5, 210 ml. of whole blood were given and the haemoglobin on October 11 was 85% (12·6 g. per 100 ml.).

Re-investigation of Twin 2, who now weighed 13 lb. 2 oz. (6 kg.), showed a haemoglobin level of 43% (6·4 g. per 100 ml.); the red blood cells, 2,410,000 per c.mm., showed marked anisocytosis and poikilocytosis, moderate polychromasia and some cells appeared as polychromatic macrocytes; the colour index was 0·89; mean cell diameter, 7·0 microns; reticulocytes, 6·4%; normoblasts, 2·5 per 100 nucleated cells; a direct Coombs test was negative; serum bilirubin was 1·2 mg. per 100 ml.; the urine contained excess urobilinogen; stools contained no occult blood and the fat content was normal. On October 6, a transfusion of 220 ml. of whole blood was given and on October 11 the haemoglobin was 109% (16·1 g. per 100 ml.).

The haemoglobin fell progressively until the patients were admitted again on December 19. Both had palpable spleens and a further investigation of Twin 1, whose weight was 15 lb. 12 oz. (7·2 kg.), showed that the haemoglobin level was 53% (7·8 g. per 100 ml.); the red cells, 3,040,000 per c.mm., showed marked anisocytosis and polychromasia, moderate poikilocytosis and anisochromia and there were some spherocytes; the colour index was 0·87; reticulocytes, 16·7%; normoblasts, 1 per 100 nucleated cells; packed cell volume, 20%; mean corpuscular haemoglobin concentration, 39%; mean cell volume 66 cu. microns, mean cell diameter (halometer) 7·0 microns, and mean cell thickness 1·7 microns; no sickle cells were detected; in a red cell fragility test haemolysis commenced at 0·6% saline and was complete at 0·32% saline; a direct Coombs test was negative; serum bilirubin was 1·0 mg. per 100 ml.; no urobilinogen was detected in the urine; radiographs of the skull and long bones were normal; a test for occult blood was negative on three occasions. On December 20, Twin 1's haemoglobin was 26% (3·9 g. per 100 ml.) and she was transfused with the packed cells of 1 pint of blood. The haemoglobin rose to 108% (16 g. per 100 ml.), but fell to 65% (9·6 g. per 100 ml.) by January 8, 1957. On January 9, a splenectomy was performed by Mr. A. R. Makey under general anaesthesia. After operation the haemoglobin level gradually rose until the baby's discharge on January 25 when it was 76% (11·1 g. per 100 ml.).

The further investigation of Twin 2, who then weighed 15 lb. 3 oz. (6,940 g.), showed a haemoglobin level of 52% (7·7 g. per 100 ml.); the red cells, 2,480,000 per c.mm., showed marked anisocytosis and polychromasia, moderate anisochromia and slight poikilocytosis and there were some spherocytes present; the colour index was 0·91; reticulocytes, 15·2%; normoblasts, 1 per 200 nucleated cells; packed cell volume, 22%; mean

corpuscular haemoglobin concentration, 35%, and the mean corpuscular volume 77 cμ; mean cell diameter (halometer), 7·0 microns, mean cell thickness, 2·0 microns; no sickle cells were detected; in a red cell fragility test haemolysis commenced at 0·56% saline and was complete at 0·32% saline; a direct Coombs test was negative; serum bilirubin was 0·8 mg. per 100 ml.; no urobilinogen was detected in the urine; radiographs of the skull and long bones were normal; a test for occult blood was negative on three occasions. On January 18 the haemoglobin level had fallen to 39% (5·8 g. per 100 ml.) and 300 ml. of packed blood cells were transfused prior to splenectomy. The patient developed an upper respiratory tract infection and splenectomy, together with the removal of an accessory spleen in the omentum by Mr. A. R. Makey, was postponed until February 25. Until the child's discharge from hospital the haemoglobin remained at about 80% (11·8 g. per 100 ml.).

On July 30, 1957, both twins were thriving, weighing 21 lb. 6 oz. (9,770 g.) and 20 lb. 1 oz. (9,170 g.) respectively, with a haemoglobin of 98-100% (14·5-14·8 g. per 100 ml.) and less than 1% reticulocytes. The osmotic fragility of the red cells of both twins commenced at 0·64% saline and was complete at 0·32% saline.

Pathology of Spleens. Dr. John Shore reported that the spleens of both twins were enlarged, measuring 7×4·5×3·5 cm. and 7·5×4·7×3·5 cm. respectively; with the latter specimen an accessory spleen, 0·8 cm. in diameter, was also received. The capsules were smooth and no abnormality was seen on the cut surfaces. The microscopical appearance of both spleens and of the accessory spleen were similar. The sinuses were filled with blood and appeared normal. A moderate amount of haemosiderin was present in macrophages in the pulp, most probably resulting from repeated blood transfusions. Scattered eosinophil and neutrophil polymorphonuclear leucocytes were also seen in the pulp. The malpighian follicles contained prominent germinal centres and also exhibited well-marked marginal zones of large and medium lymphocytes which lay between the lymphocytic mantle of many of the follicles and the pulp. Whilst not so prominent as those described in cases of hypersplenism by Leffler (1952), these zones were considerably wider than normal.

Family History. The family are all Irish and all the relatives in England were examined clinically and their haemoglobin and reticulocytes estimated and a film scanned for cells suggestive of spherocytes. The mother, father, second sister, a maternal aunt and a maternal uncle were all normal, but the oldest sister had an iron deficiency anaemia with a haemoglobin of 66% (9·8 g. per 100 ml.) which has since responded to oral ferrous sulphate. In October, 1957, a pair of binovular twins were born to the parents and these appeared clinically normal with normal haemoglobin, reticulocyte counts, red cell morphology and fragility.

Clinical Picture

Table 1 shows that a family history of congenital spherocytosis was present in 25 cases and absent in 15 cases. Thus, about 60% of the cases had a positive family history but this figure is probably too low, for the relatives of some of the patients in the table were not carefully investigated. This view is contrary to the earlier opinion expressed by Abt (1940) and David and Minot (1944) that a family history is rare if symptoms are present in infancy and indeed, only two cases (Cases 14 and 30) were diagnosed under the age of 3 months in the absence of such a history. The proportion of patients without a family history, however, is sufficiently high to make congenital spherocytosis preferable to hereditary spherocytosis as the name of the disease. The cases reported in this paper are the only identical twins in the table and the course of the disease in both was remarkably similar (Fig. 1). Debré, Lamy, Sée and Schrameck (1938) have reported identical twins both affected with congenital spherocytosis at the age of 4 years and Lesné, Launay and Hurez (1935) have described binovular twins both of whom were affected.

Of the 35 cases in the table whose sex is stated, 22 were boys and 13 girls, confirming the view that the disease is not sex linked.

Neonatal jaundice was present in 23 cases, but in Cases 1, 2 and 7 this could have been accounted for by prematurity. In Cases 32 and 38 jaundice was severe enough to produce kernikterus and in Cases 33, 38 and 43 it was sufficient to warrant one or more replacement transfusions. Turman, Vaughan and Shelley (1956) discovered another case with the clinical findings of kernikterus and a history of neonatal jaundice, when they investigated children attending a cerebral palsy clinic. A history of neonatal jaundice is also often obtained when cases are examined later in life (e.g. Campbell and Warner, 1926; Dawson, 1931; Bernard, Boiron and Estager, 1952). Neonatal jaundice due to congenital spherocytosis is accompanied by an erythroblastaemia and usually is present in the first few days after birth. In five cases, however, the jaundice did not appear until after the first week of life when haemolytic jaundice due to other causes is uncommon. Jaundice after the neonatal period was present in only six cases and was never a very prominent symptom. This fact supports the suggestion (Diamond, 1937) that the aphorism 'adults are more jaundiced than sick' should be revised to 'children, and particularly infants, are more sick than jaundiced' provided one excludes the neonatal period.

Anaemia was present in 38 cases of the 43 in the

SUMMARY OF PUBLISHED CASES OF CONGENITAL SPHE[illegible]OSIS D

No.	Source	Sex	Age at Diagnosis	Family History	Neonatal Jaundice (Days)	Subsequent J[illegible]und	Anaemi[illegible] t Obse (Age)
1	Present Cases	F	6 m.	No	4–22†	—	4 w.
2	,,	F	6 m.	No	4–22†	—	4 w.
3	Hawksley (1934)	F	2 d.	Yes	—	Slight from 4 w.	4 w.
4	Thompson (1936)	M	8 m.	—	—	Slight from 2 m.	8 m.
5	Diamond (1937)	F	4½ m.	No	—	Slight at 4 m.	2½ m
6	,,	M	6 m.	No	—	Slight at 5 m.	4½ m
7	Debré *et al.* (1938)	M	4 m.	Yes	Yes†	—	4 m.
8	Josephs (1938)	—	5 m.	—	1–14	—	5 m.
9	Abt (1940)	M	4 m.	No	—	Slight at 4 m.	4 m.
10	,,	F	1 y.	No	—	Slight at 1 y.	1 y.
11	,,	M	1 y.	No	Yes	Yes	4 m.
12	Fallon (1943)	M	2 m.	Yes	—	Slight at 2 m.	2 m.
13	,,	F	4 m.	Yes	—	At 2 m.	4 m.
14	,,	F	12 d.	No	From 12	—	12 d.
15	David and Minot (1944)	M	4½ m.	No	—	—	4½ m
16	Conrad and Schmidt (1946)	M	17 d.	Yes	From 15	—	17 d.
17	Pinckney (1946)	M	6 m.	Yes	—	—	6 m.
18	Macauley (1951	F	6 d.	Yes	—	—	17 d.
19	Newns (1951	—	3½ m.	Yes	1–14	—	2 w.
20	,,	F	7 m.	No	At 9	—	10 d.
21	,,	F	1 m.	Yes	—	—	2½ w
22	,,	M	1 y.	No	From 1	—	10 d.
23	,,	—	1 y.	Yes	—	—	1 y.
24	,,	—	10 m.	No	—	—	10 m.
25	,,	—	1 y.	No	Yes	—	1 y.
26	King and Shumacker (1952)	M	3 w.	Yes	Yes	—	3 w.
27	,,	F	2 d.	Yes	On 2	—	1 w.
28	,,	M	3 d.	Yes	From 2	—	—
29	,,	M	5 m.	Yes	—	—	5 m.
30	,,	—	13 d.	No	From 8	—	—
31	Evans *et al.* (1954)	—	7 w.	Yes	—	—	7 w.
32	Hindman (1954)	M	2 m.	Yes	Kernikterus 1–12	—	13 d.
33	,,	F	3 d.	Yes	From 2‡	—	—
34	,,	—	3 d.	—	On 3	—	—
35	Edwards and Heaton (1955)	M	4 w	Yes	4 (w.)	—	1 m.
36	Field and Tan (1955)	M	2 m.	Yes	—	—	2 m.
37	,,	F	4 m.	Yes	—	—	4 m.
38	Betke (1956)	M	4 d.	Yes	Kernikterus ‡ from 3	—	5 w.
39	Stenstrom and Ford (1956)	M	—	Yes	Yes	—	Birth
40	,,	M	—	Yes	Yes	—	Birth
41	Robinson (1957)	M	3 m.	No	—	—	4 w.
42	Shapiro *et al.* (1957)	M	2 d.	Yes	—	—	2 w.
43	Smith and Franklin (1957)	M	3 d.	Yes	From 2*	—	—

The spleen was not palpable in Cases 19, 32, 37 and 42. * Exchange transfusions on 3rd and 4th days. † Premature [illegible]xchang

table. In a further three, splenectomy was performed in the first 15 days, and in another at 10 weeks. The remaining case (Case 43) received two replacement transfusions on the third and fourth day of life, and did not develop anaemia in the next four months. Anaemia therefore appears to be a universal symptom of congenital spherocytosis presenting in the first year of life unless splenectomy or replacement transfusions have been performed for neonatal jaundice. Many cases, however, show no symptoms at all in infancy and Lappin (1956) reports two children of a family known to suffer from congenital spherocytosis, who have had spherocytosis and increased red cell fragility since birth but who have no enlargement of the spleen and no symptoms. The anaemia tends to be severe and many of the cases have had repeated blood transfusions in the first few months of life in a similar manner to the twins described here (Fig. 1). The anaemia may commence at any time during the first year but in the first week the haemoglobin level tended to be normal in the cases investigated, although several cases were thought to have been pale at or soon after birth.

Though the information is not included in the table itself the spleen was enlarged in 36 of the 40 cases where the state of the spleen was described. Thus in infants, as well as in later life, it is uncommon to find the spleen impalpable (Dacie, 1954a).

The characteristic features of the blood examination are reticulocytosis, which was observed in 20 cases, and the presence of spherocytes (not detailed in the table) in 26 cases. In many cases the

SPHEROCYTOSIS DIAGNOSED DURING THE FIRST YEAR OF LIFE

Jaundice at Observed (Age)	Anaemia at Observed (Age)	Highest Recorded Reticulocyte Level (%)	Osmotic Fragility	Splenectomy (Age)	Follow-up and Comments
—	4 w.	19·0	Increased at 9 m.	9 m.	Thriving, 19 m.
—	4 w.	16·7	Normal at 4 m.; increased at 9 m.	11 m.	Thriving, 19 m.
from 4 w	4 w.	13·4	Increased at 2 d.	—	Diagnosed by increased fragility before symptoms appeared.
from 2 m	8 m.	10·0	Increased at 8 m.	—	—
at 4 m.	2½ m.	31·0	Increased at 4½ m.	4½ m.	Thriving, 4 y. (Diamond, 1938.)
at 5 m.	4½ m.	80·0	Increased at 6 m.	—	Died before treatment.
—	4 m.	12·0	—	—	Died of otitis, 4 m.
—	5 m.	15·0	—	—	—
at 4 m.	4 m.	35·0	Normal at 4 m.	—	Thriving, 14 m. without splenectomy.
t at 1 y.	1 y.	25·0	Increased at 1 y.	15 m.	Thriving, 3 y.
es	4 m.	34·0	Normal at 1 y.	2½ y.	Thriving, 4½ y.
at 2 m.	2 m.	11·0	Normal at 2 m.; increased at 2½ y.	2½ y.	—
2 m.	4 m.	—	Increased at 4 m.	22 m.	Complete recovery.
—	12 d.	—	—	2 m.	Recovery not complete; 4 transfusions before 2 m.
—	4½ m.	32·0	Normal at 4½ m.	5 m.	Thriving, 8 m.
—	17 d.	60·0	Increased at 17 d.	2½ m.	Thriving, 5 m.
—	6 m.	30·0	Increased at 6 m.	7 m.	—
—	17 d.	5·0	Increased on 6th d.	—	2 transfusions before 6 w.
—	2 w.	—	Increased	—	—
—	10 d.	—	Normal in 1st y.; increased at 8 y.	10 m.	Thriving, 7 y. after splenectomy.
—	2½ w.	—	Slightly increased	2 m.	Died bronchopneumonia and suprarenal haemorrhage, 3½ m.
—	10 d.	—	Normal at birth; increased later	3½ y	—
—	1 y.	—	Increased at 1 y.	—	No symptoms.
—	10 m.	—	Increased at 10 m.	—	—
—	1 y.	—	—	—	—
—	3 w.	—	Increased at 3 w.	4 w.	Meningococcal meningitis, 12 m.
—	1 w.	—	Increased	3 w.	Meningitis, 6 m.
—	—	—	Increased	2 w.	Died, meningococcal septicaemia, 8½ m.
—	5 m.	—	Increased at 5 m.	6 m.	*H. influenzae* meningitis, 3½ y.
—	—	—	Increased	2½ m.	Died, septicaemia, 3½ m.
—	7 w.	—	—	9 w.	Meningococcal meningitis 6 m. after splenectomy.
—	13 d.	5·8	Increased at 2 m.	2 m.	At 2 y. has permanent neurological damage due to kernikterus.
—	—	—	—	5 d.	Thriving, 1 y.
—	—	—	—	3 d.	—
—	1 m.	—	Increased at 1 m.	1 m.	Thriving, 7 y.
—	2 m.	—	Increased at 2 m.	—	Unable walk at 2 y. No treatment.
—	4 m.	—	—	—	—
—	5 w.	17·0	Increased at 4 d.	—	Anaemia but no jaundice at 4 m.
—	Birth	—	Increased	16 m.	—
—	Birth	—	—	11 m.	—
—	4 w.	8·8	Normal at 4 m.; increased at 5 m.	7 m.	Pneumococcal meningitis, 9 m.
—	2 w.	13·6	Increased at 2 m.	—	Thriving, 7 m.
—	—	—	Increased on 3rd d.	—	Thriving. 4 m.

mature — xchange transfusion on 4th day.

reticulocytosis was marked and in the second case of Diamond (1937) it reached 80%. This was often accompanied by normoblastaemia which reached 40% of total nucleated cells in Case 5. The spherocytes can usually be identified in blood films stained with a Romanowsky dye as small deeply staining cells and the presence of larger thinner reticulocytes produces the anisocytosis and polychromasia which are frequently observed. In cases of congenital spherocytosis the mean cell diameter and the mean cell volume are smaller than usual, and the mean cell thickness is greater than normal. The changes, however, are usually not sufficiently abnormal to be of aid in substantiating the diagnosis (Young, Izzo and Platzer, 1951).

The osmotic fragility of the red blood cells was recorded in 34 cases and was normal in three cases and increased in the other 31. In five of these 31 cases the fragility was normal when first examined and increased later. In nine of the 26 cases with increased fragility on the first examination, the increase was noted in the first month of life. It is thus probably untrue that the red cell fragility may not be abnormal in infancy (David and Minot, 1944) but to demonstrate the abnormality may require a more careful technique including incubated red cell fragility, auto-haemolysis and mechanical fragility. These techniques are discussed by Young *et al.* (1951), and Robinson (1957) has found the incubated fragility increased at 4 months of age when the non-incubated fragility was within normal limits. The presence of spherocytes and an increased osmotic fragility in the neonatal period may, however, be associated with

erythroblastosis foetalis due to ABO incompatibility (Crawford, Cutbush and Mollison, 1953).

The twins reported in this paper demonstrated all of the features which have been shown above to be typical of congenital spherocytosis in infancy. Although there was no family history of spherocytosis, the fact that both identical twins were affected strongly suggests that the disorder was a congenital one. They developed neonatal jaundice and subsequently a recurrent anaemia without jaundice. Their spleens were enlarged and blood examination showed the presence of spherocytes, reticulocytes and normoblasts, and the osmotic fragility of the cells was increased. Splenectomy dramatically relieved the recurring anaemia although the fragility of the red cells remained abnormal.

Management

Spencer Wells performed the first splenectomy in a case of congenital spherocytosis in 1887. Forty years later Dawson (1931) was able to make the diagnosis in retrospect by demonstrating the typical haematological picture in Spencer Wells' patient who was then completely symptom free. This demonstrates the effectiveness of the operation and today most authorities agree with Dacie (1954b) that the results of operation are so good and the mortality so low that the operation should be carried out in all patients except in the completely compensated and symptom-free cases. There are some who would go further (e.g. Young, 1955) and advise splenectomy even in the absence of symptoms.

However, recently evidence has accumulated to show that splenectomized children and infants have an increased susceptibility to infection, particularly to pneumococcal meningitis (Smith, Erlandson, Schulman and Stern, 1957). King and Shumacker (1952) thought that this association was restricted to children in the first 6 months of life, but the patients described by Smith *et al.* (1957) ranged in age from 13 months to 17 years at the time of splenectomy. Eight of the 21 children in Table 1 who had a splenectomy in the first year of life developed a serious infection post-operatively, and three of these died. Walter and Chaffin (1955) mention 10 cases of congenital spherocytosis treated in the first year of life by splenectomy and the only post-operative infection was a case of otitis media. Gofstein and Gellis (1956) discuss 17 cases of splenectomy for congenital spherocytosis under the age of 1 year and only one of their patients developed an infection, a fatal tracheo-bronchitis. By totalling from these three sources the incidence of infection following splenectomy for congenital spherocytosis in the first year of life, we find that 10, 21%, of 48 patients developed an infection and 4, 8%, died (Table 2). I have only been able to find one record of a patient developing an infection after splenectomy for this disease later in life (Gofstein and Gellis, 1956). As far as present knowledge allows any conclusion to be made, the risk of infection following splenectomy in congenital spherocytosis appears to be confined to infancy, but it must be emphasized that this age distribution is not the experience of Smith *et al.* (1957) with splenectomy performed for other conditions. Although the evidence is by no means conclusive, it is probably wise to delay splenectomy as long as possible when congenital spherocytosis occurs in infancy. The management then resolves itself into the treatment of neonatal jaundice and anaemia later in infancy.

TABLE 2

INCIDENCE OF INFECTIONS FOLLOWING SPLENECTOMY PERFORMED IN THE FIRST YEAR OF LIFE FOR CONGENITAL SPHEROCYTOSIS

Source	No. of Cases	No. of Infections	No. of Deaths due to Infection
Table 1	21	8	3
Walter and Chaffin (1955)	10	1	0
Gofstein and Gellis (1956)	17	1	1
Total	48 (100%)	10 (21%)	4 (8%)

The prevention of kernikterus is the aim of treatment in the first week of life. This is liable to occur whenever the serum bilirubin rises above 19 mg. per 100 ml. in cases of haemolytic disease of the newborn (Mollison and Cutbush, 1951). It is, therefore, usual to perform a second or subsequent replacement transfusion whenever the serum bilirubin rises above 20 mg. per 100 ml. and if this technique is carried out kernikterus can be prevented (Hsia, 1953). Replacement transfusion was performed in Cases 33, 38 and 43 in Table 1, but in Case 38 evidence of kernikterus was already present. In Case 33 splenectomy was performed soon after the replacement transfusion and produced a rapid fall in the serum bilirubin and in Case 34 splenectomy was performed on the third day to prevent neonatal jaundice rising to a dangerous level. Smith and Franklin (1957) performed a replacement transfusion on both the third and fourth days of life and at 4 months their infant was symptom-free. Repeated exchange transfusions whenever the serum bilirubin is approaching or above 20 mg. per 100 ml. appears

to be the treatment of choice in the hope that splenectomy may be delayed until after infancy.

If the patient presents as anaemia in infancy, then he must be carefully observed and blood transfusion advised whenever the haemoglobin level falls too low. The indication used in treating the twins was a haemoglobin level lower than 50% (7·4 g. per 100 ml.) and this prevented the development of cardiac dilatation and impairment of growth which was noted by Bernard *et al.* (1952). In these circumstances, the risks of delaying splenectomy are the development of pigment gall stones (but this has never been found in the first year of life) and the possible occurrence of a haemolytic or aplastic crisis. If the parents are advised to return to the clinic if the patient is pyrexial or unwell in any way, then the crisis can be diagnosed early and blood transfusion is likely to be life saving (Dameshek, 1941). Repeated blood transfusions will eventually lead to transfusion siderosis and this was noticed in the histological examination of the spleens of the twins in whom three transfusions each were given and splenectomy was performed at 9 and 11 months respectively.

Summary

Identical twins suffering from congenital spherocytosis in the first year of life are described and their clinical features, together with those of another 41 cases found in the literature, are tabulated.

The majority of cases occurring in infancy are found to have a positive family history and present as neonatal jaundice or recurring anaemia with an enlarged spleen. The characteristic changes in the peripheral blood are the presence of spherocytosis, a marked reticulocytosis and an increased red cell fragility.

Because of the risk of infection, splenectomy should be postponed until after infancy. Neonatal jaundice should be treated by repeated replacement transfusions and anaemia of infancy by simple blood transfusion.

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CONGENITAL HEART DISEASE IN ONE OF IDENTICAL TWINS

BY

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As so many of the diseases afflicting children have been successfully controlled, attention has been focused increasingly on congenital abnormalities.

The developing embryo can be affected by inherited genetic factors or by the environment, and twins have been much studied to help in the differentiation of these factors. Identical twins, arising from the same ovum, have identical genetic structure, so that differences between them must arise from some difference in the environment.

Formerly, most congenital defects were thought to have a genetic basis, but recently environmental factors have come increasingly into prominence. Despite this, few cases of congenital malformation of the heart in one of a pair of monozygotic twins have been recorded. Such a case is described here with a summary of previously recorded examples.

Case History

Linda was seen at the age of 6 years because a heart murmur had been detected on examination during a mild attack of pneumonia one month previously. As she was a twin, her twin sister, Anne, was also sent for, and the two examined together.

The twins came sixth in the family, the five older siblings being singletons and quite healthy. An uncle of the mother had twins, a boy and a girl, among eight children, and an aunt of hers had girl twins beside two singletons. Whether these girls were identical twins or not is unknown.

The age of both the mother and father at the time of the birth of the twins was 37 years. Both parents were healthy, and the mother was not examined radiographically until the seventh month of pregnancy.

At birth, which was at term, Linda weighed 7 lb., and Anne 5½ lb., and the slight difference in size has been maintained since. Both twins were reared on National Dried Milk, and passed their developmental milestones together at the usual times.

Both children are liable to attacks of tonsillitis from which they suffer almost simultaneously, and both had a mild bout of pneumonia one month before the time of examination.

On examination, Linda weighed 44 lb. and measured 43 in. in height. (Anne 40½ lb. and 42 in.)

They were remarkably similar in appearance (Fig. 1),

FIG. 1.—The twins—Linda on the right.

and the only differences noted were the abnormalities in Linda's cardiovascular system and the fact that Anne was left-handed while Linda was right-handed.

Examination of Linda's heart showed the apex beat to be in the fifth left interspace in the nipple line. The impulse was not remarkable. There was a harsh systolic murmur and thrill maximal in the second left interspace, and the second pulmonary sound was weak. Blood pressure was 110/70. Cardioscopy showed slight enlargement of the right ventricle and dilatation of the pulmonary artery. The lung fields appeared clear. An electrocardiogram showed right axis deviation (Fig. 2*a*). She was not cyanosed and showed no finger clubbing, and a clinical diagnosis of isolated pulmonary stenosis was made. In contradistinction the heart of Anne was normal on examination. Cardioscopy revealed a normal cardiac outline and the electrocardiogram was also normal (Fig. 2*b*).

Since first being examined, both girls have remained well apart from tonsillitis.

Evidence of Monozygosity. Unfortunately the midwife who delivered the twins has since died, and no record of the delivery has been preserved. The mother stated that there was but one afterbirth, which, though suggestive, cannot be accepted as conclusive evidence, so further corroboration was sought. Using Newman's (1940) method of similarity, the following points were noted:

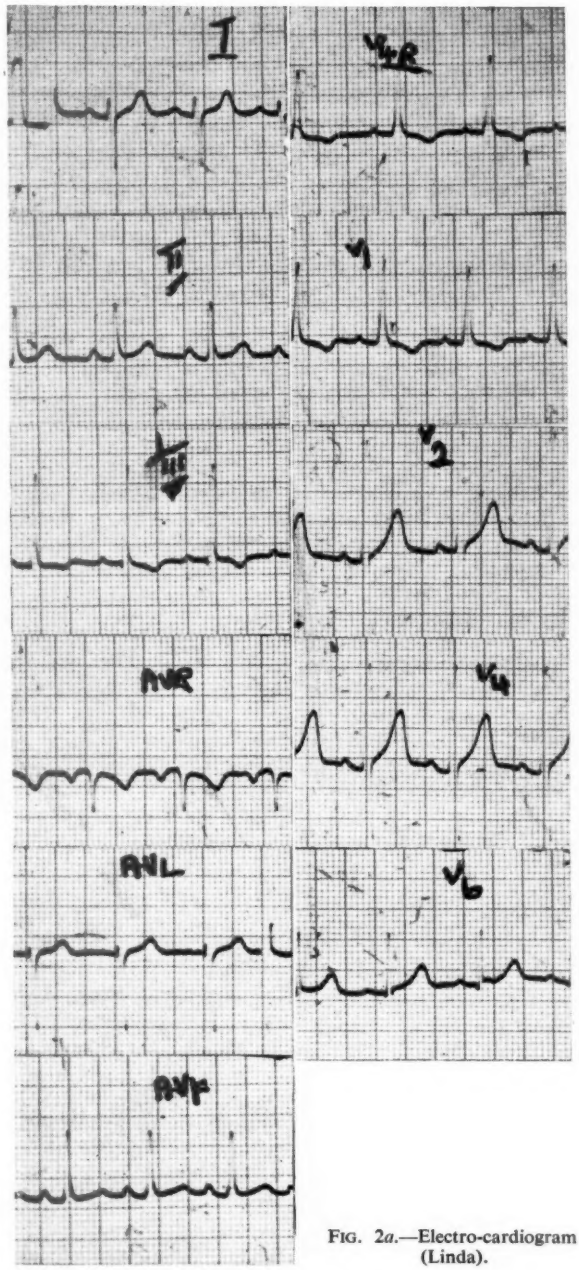

FIG. 2*a*.—Electro-cardiogram (Linda).

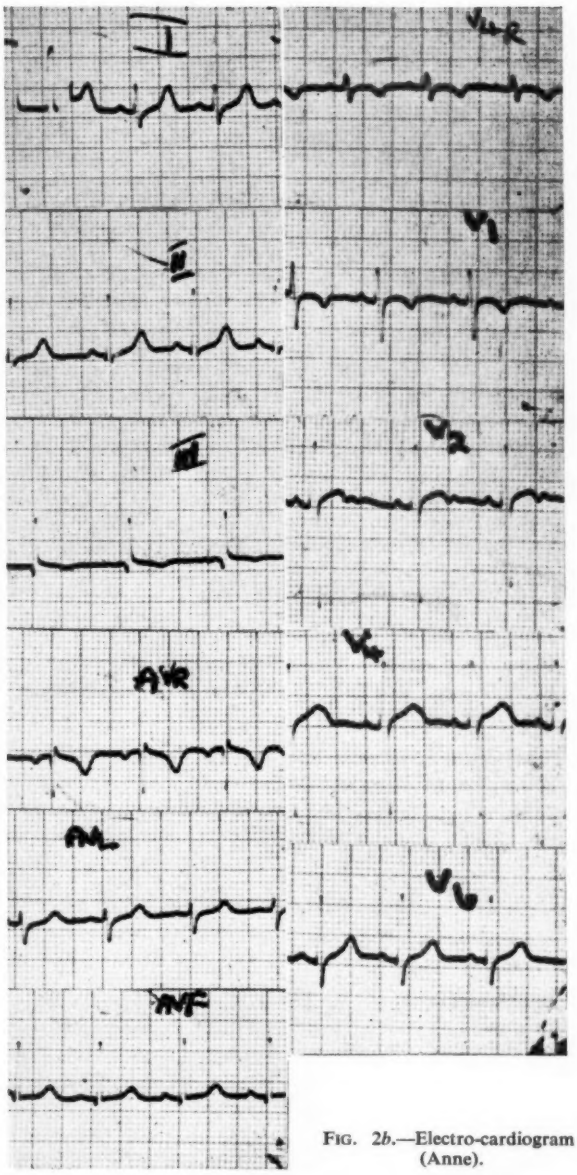

FIG. 2*b*.—Electro-cardiogram (Anne).

The features were markedly similar. The twins' hair was alike in colour, texture and whorl, as were the eyelashes. The irides were the same colour in the two girls. The lips and ears were similar. The teeth of the two were alike in appearance and time of eruption, except for one carious molar in the case of Linda.

The finger prints were interesting. The impressions of the two were remarkably similar but not identical, and the right hand of Linda resembled more closely the left hand of Anne than her own left hand.

Intelligence tests gave identical results in both girls: an intelligence quotient of 95 on Terman Merrill Form L, and a mechanical reading age (Schonell Graded Word Test) of 5·1 years.

Finally, Dr. W. Weiner, Director of the Birmingham Regional Blood Transfusion Service, kindly examined the blood of each twin, which was found to be Group AB, Rhesus negative, cdE/cde, M positive, Kell negative, in both children. He also examined the blood of the parents, siblings, two uncles, an aunt and the maternal

grandmother. He concluded from these blood studies that the degree of probability of the twins being identical was 96·4%.

On this evidence there seems no doubt that the children are indeed one egg twins.

Cases in the Literature

The following instances of congenital heart disease, recorded as occurring in one egg twins, have been found in the literature:

(1) Forsyth and Uchida (1951). A pair of 6-year-old girl twins, one of whom had an auricular septal defect diagnosed clinically and by cardiac catheterization. The evidence of monozygosity was incontrovertible and better documented than in any other of the recorded instances.

(2 and 3) Wade (1952). The first was a pair of girl twins, one of whom had a patent ductus arteriosus successfully ligated. The second was a pair of girl twins, one of whom was considered to be suffering from isolated pulmonary stenosis. Evidence of monozygosity in each pair was a marked similarity in numerous features. Moreover, the finger prints of each set of twins, although not identical, were closely similar, and there were no serological differences in the blood of each pair.

(4) Goldman and Stern (1952). A pair of male twins, one of whom, when aged 10 years, was considered on clinical, radiological and electrocardiographic evidence to have an atrial septal defect. The twins were stated to have been monochorionic, and no other evidence of monozygosity was given.

(5) Jeune and Confavreux (1948). The second of male twins died at 11 weeks of age. He was cyanosed from soon after birth. Necropsy disclosed a persistent foramen Botalli, a ventricular septal defect and pulmonary infundibular stenosis. The evidence given in favour of monozygosity was that the twins were born in a single water sac, and that there was only one placenta. It is interesting that they had mirror image irregularities of the ears and palm prints (poor prints).

(6) Kean (1942). A pair of girl twins, examined when 18 years old. Both had complete situs inversus visceralis, confirmed by radiographs and electrocardiograms. One of the girls had organic heart disease as shown by a harsh thrill and systolic murmur to the right of the sternum, and an accentuated second sound on the right. This twin developed subacute bacterial endocarditis, caused by *Streptococcus viridans*, from which she subsequently died. Permission for necropsy was refused, but the author considered that she had suffered from congenital and not rheumatic heart disease. Evidence that they were a pair of one egg twins appears to be satisfactory. Although there were two placentas, this may happen when the twinning division takes place unusually early. Otherwise the similarity points described by Newman were well satisfied.

Although the evidence given in these six examples is not always complete, there seems little doubt that each pair was identical. There are, however, a few case records which, for one reason or another, cannot be definitely accepted.

(7) McClintock (1945). A female infant, the second of twins, birth weight 4½ lb., died on the fourth day. Necropsy revealed a patent ductus arteriosus and coarctation of the aorta. The other twin girl survived and was clinically normal. The only evidence of monozygosity was the presence of one placenta.

(8) Dubreuil-Chambardel (1927) described briefly a pair of twins ('identité parfaite'), one of whom had complete situs inversus visceralis, confirmed radiologically. In addition, each twin had mirror-image hare lip. Most subsequent authors have quoted this pair as an example of congenital heart disease in one of identical twins, but 'mirror imaging' in varying degree was stated by Newman to occur in about one quarter of one egg twins, although situs inversus was considered to be rare. He suggested that such a reversal might be accounted for by the twinning division occurring late in development when the two half embryos had become different in their rates of development and dominance was already present. It would seem therefore that the dextrocardia in this case was inherent in the twinning process.

(9) Reinhardt (1912) gave good evidence that a pair of twins aged 20 years, who were examined for military service, were identical. Both had dextrocardia. On clinical and radiological evidence one was regarded as having some organic cardiac lesion, type unspecified, and he was given light duties.

(10) Pezzi and Carugati (1924) described young adult twins, considered to be identical, both of whom were said to have isolated dextrocardia. The evidence is confusing (for instance the liver in one of them was stated to be palpable on the left side), but the published electrocardiograms of both twins were typical of dextrocardia. In view of Newman's writings on mirror imaging in identical twins, mentioned above, one might regard this pair as having dissimilar cardiac status.

(11) Weitz (1936) in the first edition of his book, *Die Vererbung innerer Krankheiten*, described identical twins, one of whom suffered from patent ductus arteriosus. Unfortunately I have been unable to obtain a copy of this first edition, and the second edition (1949) contains no such description.

Discussion

Reading the case records of the patients cited above, one is not always certain whether the twins were of the one or two egg variety. Newman (1940) stated that if the pair are similar in appearance, and in such points as hair texture, colour and whorl, colour of eyes, shape of lips and ears, eruption and appearance of teeth, appearance of eyebrows and eyelashes, and similarity of palm and finger prints, then it is practically certain that the pair are one egg

twins. Two egg twins who are much alike always have definite differences in some of these features. The diagnosis of monozygosity by examination of the foetal membranes is not considered infallible to-day, but, if careful examination shows the presence of only one chorion, then the one egg type of twins can be assumed.

In some of the patients, the type of heart disease is not known for certain. However, it seems probable that the first six cases fulfil the requirements necessary for a diagnosis of congenital heart disease in one egg twins. Four of the remaining five are not considered completely acceptable, usually because of insufficient evidence as to the type of twinning and the kind of heart disease. The final case has not been traced.

The type of heart lesion found was varied, and these examples provide evidence of the importance of environment in the causation of congenital heart disease.

Summary

A case of congenital heart disease in one of a pair of identical twins has been described.

A brief account of other recorded examples has been given.

I am indebted to Dr. J. C. Ford, Consultant Pathologist, for help, to Dr. M. Shields for kindly performing the intelligence tests, and to Mr. D. R. Paton for the photographs.

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THE ELECTROCARDIOGRAPHIC RECOGNITION OF VENTRICULAR HYPERTROPHY IN CONGENITAL CARDIOVASCULAR DISEASE DURING THE FIRST YEAR OF LIFE

BY

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The value of electrocardiography in the elucidation of the diagnostic problems of congenital heart disease in infancy has been limited by lack of precise knowledge of normal features of the electrocardiogram in this age group. Battro and Mendy (1946) were the first to relate electrocardiographic patterns to age. Alimurung, Joseph, Nadas and Massell (1951) and Ziegler (1951) made detailed studies on large groups of infants and children, and their work provides standards of normality for all ages from birth to 14 years.

Publications about the electrocardiographic recognition of ventricular hypertrophy in infants are few. In these communications the existence of ventricular hypertrophy is inferred from the nature of the cardiac malformation, diagnosis being established by cardiac catheterization or contrast radiography. By these methods hypertrophy of the right ventricle may be reliably deduced, but as the techniques provide less information about the state of the left ventricle it may not be possible to distinguish between isolated right ventricular hypertrophy and combined ventricular hypertrophy.

It is the purpose of this paper to consider the value of the electrocardiogram in the determination of ventricular hypertrophy resulting from congenital cardiovascular disease in the first year of life, the type of ventricular hypertrophy and the nature of the malformation being proved by necropsy.

Investigation

Material. Forty infants were studied. Ages ranged from 2 days to 11 months at the time electrocardiograms were made. The majority of infants died within 6 months of birth. Tracings were obtained within two months of death in all cases except two, of these one child died at the age of 3 years, the other at 14 months. In 25 cases the cardiovascular lesion was one causing persistent cyanosis.

Method. In all cases standard limb leads, unipolar extremity leads and precordial leads V1, V2, V4 and V6 were used. A precordial electrode of small surface area (diameter 1·7 cm.) was employed. The recording instrument was standardized before each tracing was made.

In the interpretation of tracings the following criteria were used. The R deflection was considered abnormal if in excess of the 99·5 percentile of observed or computed maximum for age (by the standards of Ziegler (1951)). The intrinsicoid deflection in V1 was considered to be delayed if occurring 0·04 second or longer after the beginning of the QRS complex in this lead (Goodwin, 1952).

Necropsy examinations were made in all cases. Ventricular hypertrophy was invariably present. In not all cases was the heart detached from other thoracic viscera for weighing, but when this was done, heart weights ranged from 150% to 340% of that normal for age (by the standards of Potter and Adair (1940)). Cases were grouped as isolated right ventricular hypertrophy, isolated left ventricular hypertrophy, or combined ventricular hypertrophy on the basis of necropsy findings. The major cardiovascular defect in each group was as follows:

ISOLATED RIGHT VENTRICULAR HYPERTROPHY. (Total 20 cases.) Tetralogy of Fallot (6), single ventricle (3), complete transposition of the great vessels and pulmonary atresia (1), coarctation of aorta proximal to patent ductus arteriosus (2), mitral stenosis (1), isolated pulmonary stenosis (1), atrial septal defect (3), ventricular septal defect (1), congenital tricuspid incompetence (2).

ISOLATED LEFT VENTRICULAR HYPERTROPHY. (Total 3 cases.) Tricuspid atresia (2), tricuspid stenosis (1).

COMBINED VENTRICULAR HYPERTROPHY. (Total 17 cases.) Complete transposition of the great vessels (6), persistent truncus arteriosus (1), coarctation of aorta proximal to patent ductus arteriosus

TABLE 1
PATTERN OF QRS COMPLEX IN PRECORDIAL LEAD V1

Ventricular Hypertrophy	QRS Pattern									
	qR	qRS	rsR′	R	RsR′	RR′	Rs	RS	rS	Totals
Isolated right	2	1	2	11	0	0	2	2	0	20
Combined	0	0	0	0	1	1	8	6	1	17
Isolated left	0	0	0	0	0	0	0	0	3	3
Totals	2	1	2	11	1	1	10	8	4	40

(1), endocardial fibro-elastosis (2), patent ductus arteriosus (2), persistent common atrio-ventricular canal (2), ventricular septal defect (3).

Results

Ventricular Complex in V1. The types of QRS complex observed are tabulated in Table 1. In the two instances in which a qR pattern was present in V1, the complex in V2 was composed of a double peaked R and the intrinsicoid deflection was delayed in this lead. The solitary example of a qRS deflection was provided by a heart with single ventricle. In this case an rss′ pattern was present in V2.

Complexes of type R, often slurred or notched on the upstroke, were observed only in cases of isolated right ventricular hypertrophy. In 14 of 17 cases of combined ventricular hypertrophy the ventricular complex was of form Rs or RS. An rS pattern was seen only with hypertrophy of the left ventricle, whether isolated or combined.

Cases of isolated right ventricular hypertrophy could be classified in three groups on the basis of the form of the QRS complex, the amplitude of R, and the polarity of the T wave.

In the first group, of 11 cases, the intrinsicoid deflection was delayed. In 10 of these cases T was negative. In seven R was of abnormally great amplitude. This group showed incomplete right bundle branch block patterns suggesting diastolic overloading of the right ventricle (Cabrera and Monroy, 1952).

In the second group, of six cases, the ventricular complex was formed of a solitary R deflection of normal amplitude and the intrinsicoid deflection was not delayed. T was upright in four cases (abnormal in infancy except during the first 2 days of life), was isoelectric in one, and negative in one.

The third group of three cases showed features of extreme clockwise rotation of the heart, there being an initial q deflection. T was negative.

Of the 17 cases of combined ventricular hypertrophy, an incomplete right bundle branch block pattern with delay of the intrinsicoid deflection was present in 10. In four of these R was of abnormally great amplitude. Of the remaining seven cases R was abnormally tall in three.

Accepting as evidence of right ventricular hypertrophy either an amplitude of R in excess of that normal for age, or delay of the intrinsicoid deflection, the condition could be detected in 11 of 17 cases (65%) of isolated right ventricular hypertrophy (excluding from this analysis the three cases with q deflections), and in 13 of 17 cases (75%) of combined ventricular hypertrophy.

Ventricular Complex in V6. R was of amplitude in excess of that normal for age in one of three cases of isolated left ventricular hypertrophy, and in six of 17 cases of combined ventricular hypertrophy (Table 2). Delay of the intrinsicoid deflection was not of help in detecting left ventricular hypertrophy since in one case only did the intrinsicoid deflection occur after 0·04 sec., and in this case R was of abnormally great amplitude.

TABLE 2
CORRELATION OF ELECTROCARDIOGRAPHIC EVIDENCE OF VENTRICULAR HYPERTROPHY, BASED ON ABNORMAL MEASUREMENTS OF VENTRICULAR COMPLEXES IN V1 AND V6, WITH ANATOMICAL FINDINGS. (THE MEASUREMENTS WERE AMPLITUDE OF R AND TIME OF ONSET OF INTRINSICOID DEFLECTION.)

Ventricular Hypertrophy	E.C.G. Indication of Ventricular Hypertrophy				
	Right Alone	Right and Left	Left Alone	Normal Measurement	Totals
Isolated right	11	0	0	6	17*
Combined	8	5	1	3	17
Isolated left	0	0	1	2	3
Totals	19	5	2	11	37*

* 3 cases with qR or qRS patterns in V1 excluded.

Ventricular Complex in VR. Extremity leads provide less direct evidence of ventricular hypertrophy than do precordial leads. VR was studied in the hope that it might provide information helpful in making distinction between isolated right ventricular hypertrophy and combined ventricular hypertrophy when the precordial electro-

TABLE 3
PATTERNS OF QRS COMPLEX IN VR

Ventricular Hypertrophy	QRS Pattern									
	QR	QRs	qR	qRs	R	rsR′	rSR′	rSrs	rS	Totals
Isolated right	4	1	3	4	2	2	2	2	0	20
Combined	0	0	5	0	0	4	4	2	2	17
Isolated left	0	0	0	0	0	0	0	0	3	3
Totals	4	1	8	4	2	6	6	4	5	40

cardiogram indicated hypertrophy of the right ventricle alone.

Patterns of the ventricular complex are analysed in Table 3. Prominent Q deflections (Q more than one third the amplitude of R), or solitary R deflections, occurred only in cases of isolated right ventricular hypertrophy. When complexes of these types were present in VR, there was usually an R or qR pattern in V1. In two cases, however, a QR in VR was associated with an Rs complex in V1; in such cases VR may be helpful in distinguishing between isolated right and combined ventricular hypertrophy.

Discussion

Goodwin (1952) was the first to suggest criteria for the electrocardiographic recognition of right ventricular hypertrophy in young children. His subjects were aged from 3 to 14 years. His criteria were based on the time of onset of the intrinsicoid deflection, and on the patterns of the QRS complex in leads V1 and aVR.

Braunwald, Donoso, Sapin and Grishman (1955) found that 11 of 45 of their cases in a similar age group did not fulfil Goodwin's criteria. They studied 51 cases of presumed isolated right ventricular hypertrophy in children aged 1 to 15 years and found that 29 (57%) exhibited an R deflection in V1 of amplitude abnormal for age, and that in 26 (51%) the pre-intrinsicoid deflection time in V1 was 0·04 sec. or longer. Accepting either of these criteria 41 (80%) could be correctly diagnosed. The authors considered that these criteria were the most satisfactory then available.

Employing these criteria only 65% of my cases of isolated right ventricular hypertrophy would be recognized, though the presence of right ventricular hypertrophy could be detected in 75% of cases of combined ventricular hypertrophy (Table 2). Numbers are too small for this disparity in results to be of statistical significance. I believe, however, that these criteria may well be of less value in the recognition of isolated right ventricular hypertrophy during the first year of life than at later periods. Certain cases revealed complexes in V1 which, though normal by measurement, were of abnormal configuration, such as qR, or R with positive T; these abnormal patterns were not shown by cases of combined ventricular hypertrophy, and were associated with types of cardiovascular malformation which usually prove fatal within a few months of birth.

Ziegler (1956) described a pattern of ventricular complex in right precordial leads which he considered to be indicative of the most advanced degree of systolic overloading of the right ventricle. This pattern consists of an R deflection single or double peaked, of near 100% amplitude of RS, followed by an upright instead of inverted T, and frequently preceded by a true initial Q wave. This type of complex was observed in five of my cases; in four of these R was of normal amplitude and the intrinsicoid deflection was not delayed; the existence of right ventricular hypertrophy thus could not be detected by measurement.

Ventricular complexes in V1 of the form qR (with negative T) were considered to be always abnormal by Goodwin (1952) and by Goldberger (1953). Goodwin (1952) and Brink and Neill (1955) regarded this pattern in V1 as indicative of right ventricular hypertrophy. No example was present in the large series of normal infants and children studied by Alimurung *et al.* (1951) but Ziegler (1951) found three examples in normal infants under 3 months of age.

The two cases showing a qR pattern in V1 in my series revealed other abnormalities in the electrocardiogram, in particular the ventricular complex in V2 was composed of a double peaked R wave, the intrinsicoid deflection being delayed, a pattern which when occurring in V1 is characteristic of right ventricular hypertrophy in this age group.

Only in a minority of cases of combined ventricular hypertrophy does direct measurement of the ventricular complexes in left precordial leads provide unequivocal evidence of hypertrophy of the left ventricle. In about 50% of cases the electrocardiogram permits the recognition of right ventricular hypertrophy alone (Table 2).

Ziegler (1956) suggested that, with QRS or T

wave evidence of right ventricular hypertrophy in right precordial leads, the occurrence of T wave inversion in leads from the left side of the precordium was strong presumptive evidence of associated left ventricular hypertrophy. In my series such T wave inversion occurred only in cases in which the R deflection in V6 was of abnormally great amplitude, itself an indication of left ventricular hypertrophy.

More helpful was the configuration of the ventricular complex in V1, since patterns of the forms R or qR were encountered only in cases of isolated right ventricular hypertrophy. The form of the complex in VR may also be of some value in making distinction between isolated right and combined ventricular hypertrophy because in the latter condition QR and R patterns were not observed.

Conclusions

It is emphasized that the material forming the basis of this study is not fully representative of congenital cardiovascular disease in infancy. The methods employed in selection were such that the series is necessarily composed of the more severe types of malformation. With this qualification the following conclusions are drawn regarding electrocardiographic findings during the first 12 months of life.

In about 90% of cases of isolated right ventricular hypertrophy the ventricular complexes in V1 are abnormal. Abnormalities are of three types: (*a*) The intrinsicoid deflection is delayed to 0·04 sec. or longer and/or R is of amplitude in excess of that normal for age. (*b*) The ventricular complex is in the form of a solitary R deflection which is followed by an upright T wave. (*c*) There is an initial q deflection.

Combined ventricular hypertrophy can be recognized in about 30% of cases from the presence in V1 of an R deflection of amplitude in excess of that normal for age and/or prolongation of the intrinsicoid deflection time to 0·04 sec. or longer, together with a qR or qRs pattern in V6 in which R is of amplitude in excess of that normal for age. In about 50% of cases of combined ventricular hypertrophy the electrocardiogram reveals hypertrophy of the right ventricle alone.

When the electrocardiogram is indicative of right ventricular hypertrophy alone this is likely to be isolated if the ventricular complex in V1 is of the form qR or R, or the ventricular complex in VR is of the form QR or R.

Summary

Electrocardiograms were obtained during the first year of life from 40 infants with congenital cardiovascular disease.

The presence of isolated right ventricular hypertrophy, combined ventricular hypertrophy, or isolated left ventricular hypertrophy, was later proved by necropsy.

The value of electrocardiography in the recognition of ventricular hypertrophy, and in making distinction between isolated right ventricular hypertrophy and combined ventricular hypertrophy, is discussed.

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THE DIFFERENTIAL DIAGNOSIS OF RHEUMATIC FEVER

BY

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Since the efficacy of continuous daily sulphonamide or penicillin administration in the prevention of attacks of rheumatic fever has now been established, and the measure recommended not only nationally but by international committees (World Health Organization, 1957), it has become increasingly important to recognize even mild cases of rheumatic fever. At the same time it is equally essential to avoid diagnosing this erroneously, since the resulting continuous daily prophylaxis is undesirable from the point of view both of the patient and of the tax-payer. We thought therefore that an account of our observations at this National Centre for Juvenile Rheumatism over the last nine years would be useful, since over this period there has accumulated considerable experience not only of rheumatic fever, but also of many conditions which masquerade as such.

Out of such prolonged experience at the House of the Good Samaritan in Boston, Duckett Jones (1944) was able to formulate a set of diagnostic criteria which have proved extremely useful in a modified form (Rheumatic Fever Committee Joint Report, 1955) for ensuring in a large therapeutic trial that cases from many different centres were of the same general type. He realized that cases of other diseases were as far as possible to be ruled out. It was realized further that many cases of genuine rheumatic fever, if first observed late in the course of the disease, or if mild, could not be fitted in and would have to be called 'probable rheumatic fever'. Furthermore, some of the criteria depend upon continuous clinical observation or laboratory tests usually possible in hospital, but only comparatively rarely made in this country in the average general practice. In this centre then, a discharge diagnosis of rheumatic fever has been made on unformulated but rather wider grounds than those of the Duckett Jones criteria, so that of 2,214 patients admitted to the unit over the nine-year period, 959 were discharged with the diagnosis of rheumatic fever. Nearly two thirds of these satisfied diagnostic criteria comparable to those of Duckett Jones, save that chorea was excluded as a major criterion and past rheumatic fever as a minor criterion. In addition, 42 cases were discharged with a diagnosis of 'possible rheumatic fever' and 202 with a diagnosis of Still's disease, the remaining 1,011 cases being various other miscellaneous disorders.

Group A. Erroneous Initial Diagnoses in Rheumatic Fever Cases

A one-in-six sample of these patients ultimately diagnosed as rheumatic fever was taken, consisting of those with surnames beginning with the initials A, B and C admitted between July, 1947, and June, 1956. In this group of 160 rheumatic fever patients, 12 were found definitely to have been initially otherwise diagnosed, though subsequently all satisfied Duckett Jones' criteria for the diagnosis of rheumatic fever. All were children between the ages of 6 and 12 years, apart from the patient initially thought to have sub-acute bacterial endocarditis, and only in that patient and the child thought to be a case of Still's disease was the ultimate diagnosis not made before transfer here. All patients have been regularly followed up since discharge, for periods between 18 months and seven years.

Poliomyelitis. These two children complained of fever and limb pains and one had neck stiffness. Normal cerebrospinal fluid was found and in both significant heart murmurs became audible subsequently.

Pneumonia. This 9-year-old girl gave a history of general malaise and limb pains. On admission to the referring hospital, she was febrile and was found to have impaired percussion note and crepitations in the right mid-zone. Following subsidence of the chest signs she developed significant heart murmurs, and later rheumatic nodules.

Meningitis. This child had a sore throat followed by limb pain and headache. Normal cerebrospinal fluid was obtained and she subsequently developed polyarthritis and heart block.

Rubella. This 7-year-old girl had a sudden onset of abdominal pain and a rubella-like rash. There was, how-

ever, a normal white count and no accompanying lymphadenopathy; she subsequently developed pericarditis and endocarditis.

Dysentery. This girl complained of abdominal pain, diarrhoea and limb pains. Stool culture was negative. She complained of limb pains after the diarrhoea settled and an organic mitral pansystolic murmur developed.

Subacute Bacterial Endocarditis. This young adult female with known rheumatic heart disease gave a five-day history of general malaise, generalized aches and pains and fever. She subsequently developed polyarthritis and a raised antistreptolysin-0 titre; repeated blood cultures were negative and there were no embolic manifestations. She responded to bed rest and salicylates.

Appendicitis. These two children both complained of abdominal pain. Normal appendices were removed, but they both subsequently developed polyarthritis and organic heart murmurs.

Suppurative Arthritis of Hip. This 9-year-old boy had a four weeks' history of pain in one hip with inguinal adenitis and fever. He subsequently developed polyarthritis and a mitral pansystolic murmur.

Still's Disease. This boy presented with a three months' history of polyarthritis, fever, rash and general malaise. It was not until after 10 weeks in this hospital that he developed heart lesions, by which time the arthritis had settled leaving no residua.

Fallen Arches. This 6-year-old boy had complained of pain in his feet for four weeks and had been treated with remedial exercises. He developed polyarthritis, and had a raised E.S.R. and A.S.O. titre.

Group B. Unsubstantiated Admission Diagnosis of Rheumatic Fever

This group consisted of all patients admitted between July, 1947, and October 31, 1956, with the presumed diagnosis of rheumatic fever, but in whom this diagnosis was not substantiated. Only those were included in whom there was fairly certain evidence from the referring letter or history on entry that they were thought to have rheumatic fever; they numbered 196.

These 196 admissions consisted of 171 children under the age of 17 years, and 25 adults. Follow-up has varied from none in a small minority to several years in some instances. There has been no evident rheumatic activity at these check-ups, and no patient has developed organic heart disease under out-patient observation. None of the patients either on long or short term follow-up has been re-admitted with rheumatic fever. They may be divided into seven broad groups which can be further subdivided as shown in Table 1. The various groups will now be considered in more detail:

TABLE 1

FINAL DIAGNOSIS OF 196 CASES REFERRED AS RHEUMATIC FEVER IN WHOM THIS DIAGNOSIS WAS NOT CONFIRMED

Functional (8):	
Physiological tachycardia	3
Hysteria	3
Neurosis and depression	2
Traumatic and Postural (11):	
Sprains	5
Slipped femoral epiphysis	2
Torn cartilage, osteochondritis dissecans, chest deformity and back ache—1 each	4
Infections (91):	
Upper respiratory tract	45
Lower respiratory tract	10
Bone and joint	10
Blood stream	4
Urinary tract	4
Pericarditis	2
Specific fevers	16
Connective Tissue Disorders (42):	
Still's and rheumatoid arthritis	24
Schonlein-Henoch purpura	8
Erythema nodosum	5
Visceral lupus erythematosus	2
Periarteritis nodosum	1
Penicillin sensitivity	1
Granuloma annulare	1
Rheumatic and Congenital Heart Disease (9):	
Congenital	2
Rheumatic	7
Blood Dyscrasias (2):	
Iron deficiency anaemia	1
Aleukaemic stem-celled leukaemia	1
Others (33):	
Arthritis	5
Arthralgia	9
Limb pains	15
Fever	3
Gout and syphilis	1
Total	196

I. Functional. This group comprised six children and two young adults. The three patients with physiological tachycardia were all children. The first had a history of recent sore throat and the referring doctor thought he had detected clinical signs of cardiac enlargement with persistent tachycardia. The second child had complained of limb pains for six weeks and was noted to have an evening temperature up to 98·8°F. and persistent tachycardia of 130-140 per minute. The third child had a recent history of cold and cough with persistent tachycardia. Nothing abnormal could be found in any of these patients, and, although the pulse rate was elevated by day, the sleeping pulse was within the normal range (Nelson, 1954).

The two young female adults complained of limb pains and general ill-health; one had had rheumatic fever as a child; she showed hysterical manifestations such as hyperventilation and no organic signs were found. The other patient also had nothing organic demonstrable, and was referred to a psychiatrist who diagnosed neurosis and depression.

The other three children all complained of pains in joints or limbs for which no organic cause was found. One had a functional wrist drop, the second hysterical gait, and the third, with an unhappy home background, admitted to exaggerating his symptoms

because of desire for sympathy. All were helped by psychiatric treatment.

II. Traumatic and Postural. All the patients in this group were children, and all complained of joint pains; three patients had a history of rheumatic fever. In eight patients there was a definite history of trauma with objective signs in a single joint (knee in three cases, ankle in two, hip in two and elbow in one) with radiological evidence of slipped epiphysis in the two patients with hip involvement and of osteochondritis dissecans in the patient with elbow involvement. In the other five patients, there were normal serological findings, normal hearts and absence of other joint involvement. One patient gave a history of rheumatic fever previously, and of recent joint pains, low grade fever and suspected presystolic murmur; she was found to have a normal heart and normal temperature range, but a considerable degree of sternal deformity and scoliosis. Another girl had also had rheumatic fever and complained of pains in her back and thighs. No signs of rheumatic activity were found, but the backache was thought to be postural following her period of prolonged bedrest. The last patient gave a history of painful swelling of both knees following a sore throat. She had a normal heart and there was no evidence of rheumatic activity. Both knees tended to lock in flexion and to extend suddenly with a click, suggesting meniscus lesions. Exploration of the knee joints revealed torn cartilages, which were thought to be due to a congenital defect.

Slipped Femoral Epiphysis. (i) This girl, aged 13, was referred with the following letter from her family doctor, 'Rheumatic fever 18 months ago. Now complains of pain in joints, right foot swollen. Systolic murmur at apex which has just appeared. I should be grateful if you would take her in for recurrence of rheumatic fever'. The history obtained on transfer here was of trauma to the right thigh one month previously, since when she had limped and noticed pain in the feet, knee and hip on the affected side, with recent swelling of the foot. On examination, movements of the right hip were restricted and painful and there was slight swelling of the right foot. A radiograph of the right hip showed slipped femoral epiphysis. There was evidence of mitral and aortic valve disease but this was thought to be inactive and she was transferred to an orthopaedic hospital for operation. She has now been followed up for five years and there has been no fresh rheumatic activity.

(ii) J.H., aged 14, was admitted with painful swelling of the elbow for two weeks. He had had rheumatic fever with carditis two years previously. After admission no further joints became involved and there was no evidence of recent streptococcal infection or carditis; but radiography showed osteochondritis dissecans affecting the capitellum.

III. Infections. (*a*) Upper Respiratory Tract Infections. Of this large group, 45 (43 children and two young adults) were diagnosed as upper respiratory tract infections. The presumptive diagnosis of rheumatic fever was based on preceding upper respiratory tract infection followed by limb or joint pains, fever and general malaise in 33 patients. There were 12 patients in the whole group who did not complain of pain and in eight of them an organic systolic murmur was initially suspected, as in 16 of those who did complain of limb and joint pains. Three had had previous rheumatic fever. In all these patients, rheumatic activity was thought unlikely because of the absence of abnormal physical signs other than those of a present upper respiratory tract infection in some cases, and because of normal or rapidly settling sedimentation rate and negative evidence of streptococcal infection, except for two children (one with raised A.S.T.) whose throat swabs grew group A haemolytic streptococci.

(*b*) Lower Respiratory Tract Infections. All these patients were children and the typical symptomatology differed from the upper respiratory tract group in that fever and cough were the presenting symptoms; pain, complained of by four children, was confined to chest or shoulder. Two children (one with primary tuberculosis and the other with bronchiectasis) had persistently elevated sedimentation rates and in four patients an organic systolic murmur was queried but not confirmed here. There was radiological proof of diagnosis in six cases (two, primary tuberculosis; one, bronchiectasis and three, lobar pneumonia). The remaining four children were diagnosed as bronchitis or resolving pneumonia in view of the chest signs on admission and the absence of cardiac involvement or streptococcal infection.

Left Lower Lobe Pneumonia. This girl, aged 8, had had rheumatic fever and chorea five years previously. She had a sore throat one week before present admission followed by general malaise and fever. Her doctor queried precordial friction rub and thought she had had a relapse of acute rheumatism. This was not confirmed here but there were early signs of pneumonia at the left base and a subsequent radiograph showed consolidation of the left lower lobe. She responded to penicillin therapy.

(*c*) Bone and Joint Infections. Four of these 10 patients (nine children and a young adult male) complained of multiple joint pains and fever, but subjective and objective signs eventually became localised to one joint and diagnosis was confirmed by obtaining pus on drilling or by periosteal changes on radiographic examination. The six other patients had pain and swelling of a single joint with fever, and diagnostic proof by aspiration of purulent fluid in five cases and radiological changes in three (periostitis in two and Brodie's abscess in the third).

J.W., aged 15, was admitted to another hospital with fever and pain in the right knee. White blood cells were 8,000 per c.mm. with 80% polymorphs. Osteomyelitis was queried and she was given a short course of penicillin, but she then developed pain in other joints and was thought to have rheumatic fever. She was put on to salicylates and transferred here. She continued to run a low grade pyrexia and high E.S.R. and a bony swelling of the lower end of the right femur became apparent. White blood cells at this time were 5,000 per c.mm. with 50% polymorphs. Radiographs showed marked bony changes of osteomyelitis and the femur was subsequently drilled.

(*d*) BLOOD STREAM INFECTIONS. Three of these cases were children and the fourth a young adult female. All complained of multiple acute painful swollen joints, fever and general malaise. In one boy an organic mitral systolic murmur was suspected. Ultimate diagnosis was based on a positive blood culture (staphylococci in two cases and streptococci in two cases), rapid response to chemotherapy and absence of cardiac involvement.

(*e*) URINARY TRACT INFECTIONS. These four patients (all children) complained of limb pains and general malaise and were referred with low grade fever and a suspected organic systolic murmur in one case. All had *Esch. coli* urinary infections and one had a hydronephrosis. No other abnormal physical signs were found, and there was no evidence of carditis or of streptococcal infection.

(*f*) PERICARDITIS. One of these children presented with shoulder pain and fever, and the referring doctor thought that organic systolic and diastolic murmurs were present. On admission here she was found to have pericardial and pleural effusions with pericardial friction, but no evidence of endocarditis. There was no evidence of streptococcal infection. A Mantoux test at 1:1,000 was positive and radiographs showed enlarged hilar glands on one side. Symptoms and signs resolved after prolonged bed rest, and follow-up for two years showed satisfactory progress. The other child complained of general malaise and chest pain and his general practitioner found him to be febrile and thought that an organic systolic murmur was present. On admission, he had a pericardial effusion and friction rub, but no evidence of endocarditis. There was no evidence of streptococcal infection, but a Mantoux test at 1:10,000 was positive. In both these cases, the tentative diagnosis on discharge was tuberculous pericarditis, but in view of their satisfactory progress in hospital and at follow-up, in retrospect they may both have been cases of benign non-specific pericarditis.

(*g*) SPECIFIC FEVERS. This group comprised 13 children and three girls aged 18-19 years. Five children had an acute episode of fever, limb pains and general malaise. This fever settled quickly after admission, no abnormal physical signs were elicited and there was no abnormal serology. They were thought to be cases of influenza, though no serological proof of diagnosis was sought.

Four patients had a discharge diagnosis of glandular fever. They all had fever and limb pains and in two of them an organic systolic murmur was questioned by the referring doctor. They were diagnosed after development of generalized lymphadenopathy and splenomegaly, abnormal mononuclear leucocytes in the peripheral blood and a positive Paul Bunnell titre in one case. No abnormal cardiac signs were noted and findings reverted to normal quite quickly.

An example of this group was a girl, aged 10. She was admitted with a history of sore throat three weeks previously and five days' fever and joint pains. On admission here she had a fever of 99°F. but no abnormal physical signs. Erythrocyte sedimentation rate was 15 mm./hr. and a white cell count was normal. Five days after admission, a white cell count showed a relative lymphocytosis of 60% and a week later 23% abnormal mononuclears were noted in a total of 15,850 W.B.C. per c.mm. Paul Bunnell titre was positive (1:224).

Six patients had acute histories with fever and muscle and joint pains in each case, but rapidly changing physical signs, finally developing features typical of measles, poliomyelitis, meningitis (no organism isolated but response to chloramphenicol therapy), infective hepatitis, erysipelas and paratyphoid fever.

The paratyphoid fever patient, an 18-year-old girl, had had rheumatic fever previously, leaving established mitral and aortic valve lesions. She gave a three-day history of fever, headache, generalized aches and pains with vomiting and diarrhoea for two days. The doctor thought she had had fresh rheumatic activity and put her on to salicylates. On admission here, vomiting and diarrhoea was a noticeable feature, and *Paratyphosus B* was isolated from blood, urine and faeces. She responded to treatment with chloramphenicol.

The patient with poliomyelitis, aged 4 years, was referred with the following letter from the general practitioner: 'History of tonsillitis two days previously. On admission she developed severe rheumatic pains in the arms and shoulders. Refuses to move the right arm because of the pain. C.N.S., all reflexes present and equal.' On admission here she was found to be febrile with slight neck stiffness and a flaccid paralysis of the right arm. The cerebrospinal fluid showed changes consistent with poliomyelitis.

The last patient in this group, a 13-year-old boy, had an acute onset of high fever, pain and weakness in one hip. There was no evidence of cardiac involvement nor of streptococcal infection and no further joints became involved; it was thought that he might have had radiculitis of virus origin.

IV. Connective Tissue Disorders. (*a*) STILL'S DISEASE AND RHEUMATOID ARTHRITIS. These 24 cases (three of whom were over 16 years of age) all presented with joint pains and the majority had had objective joint signs prior to admission; fever and general malaise were also presenting features. Eighteen had had acute symptoms and signs for over a month prior to admission here. Persistence of 'active' joints, swinging fever and in some cases lymphadenopathy or typical Still's rash, with confirmation by biopsy of synovial membrane in less classical cases, furnished the eventual diagnosis. Of these patients, five had pericarditis and in three patients a significant systolic murmur was thought to be present by the referring doctor. This latter finding was not confirmed here. It is of interest to note that while 16 of the 18 with symptoms of over one month's duration were thought to be Still's disease on entry to this hospital, all those six with histories of under one month's duration were thought to be rheumatic fever when first admitted; underlining the considerable difficulty in the early recognition of Still's disease. The following case history illustrates this point:

J.F., aged 11. Nine days before admission here he developed pains in his thighs after playing football. Next day the left ankle and right toe became swollen and painful. The general practitioner found his E.S.R. to be 72 mm./hr. and put him on salicylates. On admission here the right big toe and left ankle were hot and swollen, and the right hip painful. E.S.R. was 60 mm./hr.; heart and electrocardiogram normal. He was thought to be a case of rheumatic fever and put on cortisone. Despite high dosage, acute arthritis persisted and the left elbow also became involved. Persistent joint involvement with soft tissue thickening and raised E.S.R. with no evidence of endocarditis, favoured the alternative diagnosis of Still's disease which has been confirmed by the subsequent progress of the patient.

(*b*) SCHONLEIN-HENOCH PURPURA. Of the eight cases with Schonlein-Henoch purpura, five had polyarthritis and three had limb pains; abdominal pain was a prominent feature in four cases. In six patients there was history of preceding upper respiratory tract infection. In all cases the diagnosis was eventually clarified by the appearance of typical petechiae.

(*c*) ERYTHEMA NODOSUM. There were two adults and three children in this group. Four patients had joint pains and two had joint swelling together with fever. All developed lesions typical of erythema nodosum and the illness settled spontaneously, without an obvious cause having been discovered. Radiographs of the chest were normal and throat and nose swabs negative with no rise in antistreptolysin-O titre. The fifth patient gave a history of severe sore throat and fever treated with sulphathiazole, and he subsequently developed lesions typical of erythema nodosum. Sulphathiazole was suggested as the provocative agent after exclusion of tuberculosis.

(*g*) GENERALIZED LUPUS ERYTHEMATOSUS. Two young females were eventually diagnosed as acute lupus erythematosus. These patients both had joint pains and pericarditis. Eventual diagnosis was made in the first patient by the development of typical skin lesions with biopsy proof and L.E. cells found in peripheral blood. In the second patient proof was eventually found at autopsy. In neither was the diagnosis obvious at the time of transfer.

(*e*) PERIARTERITIS NODOSA. In this child of 11, a sore throat was followed two weeks later by polyarthritis, fever and rash of multiform type. On transfer here she had a patchy reticular erythema, pericarditis, polyarthritis and muscle pains. Skin biopsy showed changes typical of periarteritis nodosa. Subsequent follow-up has confirmed this diagnosis.

(*f*) PROBABLE PENICILLIN SENSITIVITY. This 5-year-old boy presented with pains in his knees and swelling of his face following an upper respiratory tract infection treated with penicillin. There was no evidence of arthritis, carditis or streptococcal infection on transfer, and he was thought to be sensitive to penicillin.

(*g*) GRANULOMA ANNULARE. This patient, a 6-year-old boy, gave a history of nodules on elbows, wrists, toes and neck, and pain in his knees, for six months. On admission here he had a normal E.S.R. and antistreptolysin-O titre. Nodule biopsy resembled granuloma annulaire, though there is no record of his subsequent progress.

V. Rheumatic and Congenital Heart Disease. (*a*) CONGENITAL HEART DISEASE. These two children were referred on account of general malaise and the discovery of abnormal heart murmurs. One had signs typical of coarctation of the aorta, and the other, aged 4, was admitted with a history of a severe febrile cold following which a heart murmur had been noted. On admission here there was no evidence of rheumatic activity, but cardiovascular findings were those of patent ductus arteriosus, which was subsequently confirmed at operation two years later.

(*b*) RHEUMATIC HEART DISEASE. This group comprised six children and a 19-year-old girl, all of whom had had rheumatic fever previously with established rheumatic heart disease. The recent history was of joint or limb pains, general malaise and tachycardia. All had normal sedimentation rate, antistrepto-

ysin-O titre and sleeping pulse, and there was no evidence of active rheumatism.

VI. Blood Dyscrasias. (*a*) IRON DEFICIENCY ANAEMIA. This 14-year-old girl presented with general malaise and odd aches and pains; the referring doctor thought there was a significant heart murmur. She was found to have severe iron deficiency anaemia and an innocent basal systolic murmur. Despite full investigation, no satisfactory explanation was found other than inadequate diet.

(*b*) ALEUKAEMIC STEM-CELLED LEUKAEMIA. This 6-year-old girl was admitted from another hospital with a diagnosis of rheumatic fever. There was one month's history of general malaise with joint pains, fever, tachycardia and swelling of the left knee. E.S.R. was 32 mm./hr.; Hb., 13·8%; W.B.C., 7,000/mm^3 (polymorphs, 82%, leucocytes, 16%, monocytes, 2%). There was an unsatisfactory response to salicylates. She was thought here to be a case of rheumatic fever until, following progressive weight loss, mild generalized lymphadenopathy and anaemia, the bone marrow was examined and showed a picture of aleukaemic stem-celled leukaemia. Radiographs of the long bones showed mild generalized osteoporosis with coarse mottling.

VII. Others. This group consisted of 25 children and eight adults. In only one patient, an adult male, aged 42, could a definite diagnosis be made. He had polyarthritis and a basal diastolic murmur. These findings were confirmed here. He had a raised serum uric acid and radiological changes characteristic of gout; the Wassermann reaction was positive, accounting for the aortic incompetence. In the other 32 patients, the provisional diagnosis of rheumatic fever was not confirmed but no satisfactory alternative diagnosis could be found. Follow-up has varied from none, in a small minority, to seven years, and in no case have rheumatic fever-like episodes recurred, nor has any cardiac abnormality developed. They are grouped according to their main symptomatology as follows:

(*a*) ARTHRITIS OF UNEXPLAINED ORIGIN. These patients, four children and one young female adult, gave a history of joint swellings but had no abnormal physical signs on admission here. No evidence of streptococcal infection was found (normal antistreptolysin-O titre and negative nose and throat swabs) and normal E.S.R. Short term follow-up was satisfactory.

(*b*) ARTHRALGIA. These patients gave a history of joint pains dating over several weeks or months and when examined by the family doctor there was either a slight rise in temperature, tachycardia or a suspected organic murmur. Three patients gave a history of recent upper respiratory tract infection. Clinical and serological examinations were negative in all these patients. Short term follow-up was satisfactory.

(*c*) LIMB PAIN. These patients all complained of limb pains, four following an upper respiratory tract infection. In four cases the referring doctor queried an organic systolic murmur; another patient had had rheumatic fever previously, and in another there was a strong family history of rheumatic fever. In other patients, low grade fever and/or tachycardia were mentioned in the referring letter. When admitted here, all investigations were negative.

(*d*) FEVER. These patients were referred on account of unexplained febrile illnesses during which the general practitioner thought that an organic murmur was present. This finding was not confirmed here, and the cause of the preceding febrile episode was never established.

Observations

From the above analysis, it may be seen that many diagnoses may be confused with that of rheumatic fever. In Group B on closer study, four general categories of diagnostic errors became evident: 1. Those cases who would fulfil the Duckett Jones criteria but in whom further observation and development of fresh features provided the ultimate correct diagnosis. 2. Those who would have fulfilled the criteria if all points in the history and clinical examination could have been corroborated. 3. Those in whom there were never even questionably sufficient criteria. 4. Those in whom the diagnosis might have been rejected or the correct one established if the referring doctor had had the facilities and leisure for carrying out further investigations.

The majority in the first category are found in the connective tissue diseases, notably rheumatoid arthritis. The early acute stage of this disease closely resembles rheumatic fever, especially in children, with pericarditis, salicylate-responding pyrexia and transient joint involvement; the Rose Waaler test is usually negative. Only continued observation of the subsequent course of the disease, or the development of endocarditis, erythema marginatum or chorea provides a solution. Even chorea may be seen in acute lupus erythematosus.

The second category comprised both those in whom the referring doctor's findings were not substantiated here, or were not felt to be significant in the diagnosis of rheumatic fever, and also cases in which other points were elicited that had either been missed before or developed subsequently. In greater detail these notably concern the following:

(1) History. A careful history is an essential in the exclusion or confirmation of the less typical forms of acute rheumatism. In several instances the relationship to trauma was missed; in a large number it seemed that complaints of limb or joint pains contributed too prominently towards the proposed initial diagnosis of rheumatic fever, since they were not complained of on transfer here and did not recur. A previous history of rheumatic fever or a family history of the illness often seemed to swing the balance disproportionately in favour of a presumptive diagnosis of rheumatic fever.

(2) Fever. Temperatures of 98·8°-99·4°F. were often cited as being a significant feature. As an isolated finding in a child, this is probably of little consequence, since a normal child's temperature may often reach these levels at some time in the 24 hours.

(3) Tachycardia. This was a feature often stressed in referring letters, particularly in the group which presented primarily with limb and joint pains. Tachycardia out of proportion to the temperature has not been a common finding here, usually occurring only in those children with severe rheumatic fever or cardiac failure; in a few cases of acute rheumatism there has been a sinus bradycardia in the early stages. Even mild apprehension can cause tachycardia in a nervous child, but the sleeping pulse will be within normal range for the age group.

(4) Systolic Murmur. The presence of an organic systolic murmur was initially queried in a total of 48 patients, half of whom were in the upper respiratory tract infection group. A systolic murmur can be demonstrated in a high percentage of infants (Hallidie-Smith, unpublished work) and most normal children (Lessof and Brigden, 1957). These murmurs are usually best heard down the left sternal edge or just internal to the apex. They may be fairly localized or propagated out of the apex and up to the neck. The innocent systolic murmur never fills systole (Lessof and Brigden, 1957), and is usually maximal in early or mid systole. The character may be low pitched and musical, or rather more high pitched and blowing (Friedman, Robie and Harris, 1949). The precise aetiology of these murmurs has not been established, but they are thought to be related to flow of blood in the great vessels and are accentuated in the febrile child whose cardiac output is increased. In contrast, the organic systolic murmur is smooth and high-pitched, filling systole. It is best heard at, or just internal to, the apex, and is propagated outwards to the axilla.

The last category comprises those in whom the error of diagnosis might not have been made if the referring doctor had been able to carry out further investigations toward an alternative diagnosis, since there was often insufficient evidence for suggesting the diagnosis as it stood. The sedimentation rate is of particular value. A normal rate (less than 15 mm./hr. Westergren) at the onset of the disease, would make the diagnosis of active acute rheumatism very unlikely, although it may remain above this level for as little as two weeks. A search for evidence of a preceding streptococcal infection by isolation of the organism in throat or nose swab, or demonstration of a rise in antistreptolysin-O titre, is of some help in doubtful cases.

In other published series (McCue and Galvin, 1948; Lewy, 1952; McCue, 1954; Saslaw, Hernandez and Werblow, 1954; Wedum and Rhodes, 1955) similar points have been made about history-taking, examination and evaluation of physical signs; in each, a large proportion of cases were referred with a provisional diagnosis of rheumatic fever, which either could not be substantiated or was superseded by an alternative diagnosis, sometimes only after careful observation over a period of time. The good long-term prognosis noted in the group with upper respiratory tract infection followed by fever and limb pains is confirmed by these writers and by Kaiser (1943). In the series referred to, the overall pattern of differential diagnosis approximates to our own with certain exceptions, in part explained by the different geographical distributions of disease, e.g. sickle cell anaemia, and in part by the fact that some series only dealt with out-patient referrals. Amongst other less common diseases not listed in our series, but noted in the literature with reference to the differential diagnosis of rheumatic fever, are cat scratch fever (Lyon, 1956); meningococcaemia (Daniels, 1948); miliary tuberculosis (Freud, Weisz and Brunhofer, 1950); ascariasis (Doumer, Lorriaux and Belbenoit, 1951); juvenile hyperparathyroidism (Bogdonoff, Woods, White and Engel, 1956); Weber Christian panniculitis (Brudno, 1950); Hodgkin's disease (Paquet and Delage, 1957); berylliosis (Sprague and Hardy, 1954), sarcoidosis (Myers, Gottlieb, Mattman, Eckley and Chason, 1952); hepatitis (Martini, 1950), and irritable hip syndrome (Caravias, 1956). This last interesting entity has also been noted here. The symptoms are fever, general malaise and sudden onset of severe pain confined to the hip, all settling spontaneously and thought to be due to synovitis.

Summary

The differential diagnosis of rheumatic fever is discussed from the experience at Taplow over a nine-year-period from 1947 to 1956. The original diagnosis is reviewed in a sample of those cases

ultimately diagnosed as rheumatic fever, and 12 cases are described which were originally diagnosed otherwise.

A larger series of 196 patients is described who were originally thought to have rheumatic fever, but in whom this diagnosis was eventually not substantiated. This series is subdivided into seven main diagnostic disease groups, which are discussed in detail and illustrated. The pointers in clinical investigation that led to the eventual diagnosis are listed and common erroneous interpretations of history, fever, tachycardia and systolic murmurs are discussed.

Thus the differential diagnosis of rheumatic fever still may present considerable difficulties, particularly in its milder forms. Some of these difficulties are insurmountable. Others could be overcome by more rigid adherence to diagnostic criteria, by more critical examination of the problems presenting, and by increased awareness of the significance of the physical signs elicited. Fuller investigations at an early stage in the disease, notably sedimentation rate and a search for streptococcal infection, would be helpful in the less obvious cases.

We are indebted to Dr. Wallace Brigden, Dr. Reginald Lightwood, Dr. Gerald Thomas and Dr. Paul Wood for their guidance and participation over the years.

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A SMALL OUTBREAK OF NEONATAL MENINGITIS IN A MATERNITY UNIT

BY

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(RECEIVED FOR PUBLICATION JANUARY 1, 1958)

The enterobacteriaceae are of particular importance in infancy as a cause of meningitis. Cooke and Bell (1922) postulated that certain strains of the *coli aerogenes* group might have a special tendency to invade the meninges, and suggested that full descriptions of the organisms isolated from such cases would be of value. Again, Barrett, Rammelkamp and Worcester (1942) commented on the frequent lack of sufficient detail for accurate classification of the organisms obtained in the majority of cases. Henderson (1948), in his review of Salmonella meningitis, found that a few types of salmonellae account for the majority of cases, and he also noted that three epidemics among the newborn accounted for more than one fourth of the 147 cases he had collected. A small outbreak of three cases of meningitis occurring in a maternity hospital is described, the organism being a hitherto unidentified member of the enterobacteriaceae.

Case Histories

Each of the three cases was accommodated for a few days at 'E' Maternity Hospital, Case 1 from July 2-8, 1957, and Cases 2 and 3 from August 22-28, 1957. During this period no other babies and, as far as can be ascertained, no members of staff or patients suffered from gastro-intestinal symptoms or other infections.

Case 1. K.L., a male infant of birth weight 7 lb. 8½ oz., was born by normal delivery at 'E' Maternity Hospital on July 2, 1957. He was the ninth child of healthy parents, the other children all being alive and well. The maternal membranes had ruptured immediately before the delivery, and the mother had no symptoms of urinary, gastro-intestinal or other infection. The infant was fed on evaporated milk, taking the feeds well and behaving normally until the age of 6 days when he became drowsy and refused to suck. Four hours later, when he had a brief episode of generalized twitching, the fontanelle was bulging slightly, the head was retracted, and the rectal temperature was 101°F. The baby was transferred to Aberdeen City Hospital where lumbar puncture produced a purulent, blood-stained cerebrospinal fluid. The detailed bacteriology of cerebrospinal fluid and faeces is given below. Treatment was commenced with intramuscular penicillin and streptomycin but the infant died 14 hours after admission. The positive findings at autopsy were marked congestion of the meninges, a purulent exudate over the base of the brain and bilateral adrenal haemorrhage.

Cases 2 and 3. C.F. and R.F. were twins, born five weeks prematurely at 'A' Maternity Hospital on August 18, 1957; they were transferred to 'E' Maternity Hospital on August 22 and discharged home on August 28. R.F., twin 1, was born by spontaneous vertex delivery, weighing 6 lb. 9 oz., and C.F., twin 2, by assisted breech delivery, weighing 5 lb. 12 oz. The maternal membranes ruptured only 45 minutes before delivery, and the mother had no fever or evidence of urinary or gastro-intestinal infection.

Case 2, C.F., was admitted to the Royal Aberdeen Hospital for Sick Children at the age of 12 days with a history of vomiting once 24 hours before admission with refusal to feed thereafter. On examination he was a drowsy hypotonic infant weighing 6 lb. 3½ oz., who did not appear acutely ill, but who had an intermittent slight cyanosis of the lips and peri-oral region. The rectal temperature was 98·2°F., pulse rate 146 per minute and respirations 58 per minute. A moderate degree of jaundice was present. No evidence was found of meningeal irritation or neurological abnormality and physical examination was otherwise negative. The urine contained a small amount of a reducing substance. The cerebrospinal fluid, which was under normal pressure, was greenish-yellow and turbid, containing 1,254 leucocytes (66% polymorphonuclear) per c.mm. Numerous Gram-negative bacilli could be seen on film; details of the bacteriology of cerebrospinal fluid and faeces are given below.

TREATMENT AND PROGRESS. Treatment initially was by intramuscular chloramphenicol (500 mg. daily for 29 days) and intramuscular streptomycin (120 mg. daily for 32 days). Cortisone was given by the same route in decreasing dosage for the first two weeks commencing with 100 mg. daily; this was used in view of the experience with Case 1 and also in an unsuccessful attempt to prevent the adhesions so frequently seen in coliform meningitis. Convulsions during the first few days of the illness were

controlled by intramuscular paraldehyde. Continuous oxygen therapy was required for the first 11 days and parenteral fluids for 12 days. At the end of the third week exploration of the left lateral ventricle revealed thick creamy pus which was aspirated daily with instillation of 25 mg. streptomycin on each occasion for the next 10 days. The infant remained extremely ill, vomiting frequently and gradually losing weight, and for this reason the therapy was changed, chloramphenicol being replaced by sulphadiazine (0·75 g. daily for nine weeks) and streptomycin by polymyxin B (intrathecally 20,000 units twice per day for three days and once per day for a further nine days, and intramuscularly 25,000 units four-hourly for three days, then six-hourly for nine days). During his sixth week in the ward the vomiting ceased and his weight began to rise, but at the age of four months he is markedly retarded in his motor development. Ventriculography shows a gross degree of internal hydrocephalus of obstructive type, although the head measurements are not increasing rapidly.

The causative organism was not cultured from the cerebrospinal fluid after the initial specimen, but a Gram-negative organism was seen on direct film as late as the end of the polymyxin treatment.

Case 3, R.F., was admitted to the Royal Aberdeen Hospital for Sick Children two days after his twin brother. This twin had remained well until only four hours before admission, when his mother noticed intermittent peri-oral cyanosis. He refused part of a feed and whimpered frequently. Following her experience with the first twin, the mother sought immediate medical attention. Physical examination at the time of admission showed a mildly jaundiced, fairly healthy-looking baby of 6 lb. 4½ oz. No cyanosis was present, the fontanelle was not bulging, and there was no rigidity of the spine or head retraction. The tone of the legs was considered to be slightly increased, and the cry was rather shrill. The cerebrospinal fluid was turbid, greenish-yellow, containing 54,000 leucocytes (91% polymorphonuclear) per c.mm. The cerebrospinal protein was 280 mg. per 100 ml.; sugar, 15 mg. per 100 ml.; and chlorides, 710 mg. NaCl per 100 ml. Bacteriological details of cerebrospinal fluid and faeces are given below.

TREATMENT AND PROGRESS. Three short courses (14 days, 10 days, 10 days) were given of chloramphenicol and streptomycin with intervals of 14 days and eight days without antibiotics. The chloramphenicol was given intramuscularly (250 mg. twice daily) for the first course and orally (250 mg. six-hourly) for the two later courses. Streptomycin dosage was 120 mg. per day. Following these drugs oral sulphadiazine was administered for six weeks. Cortisone in decreasing dosage, commencing with 100 mg. daily, was also administered for the first 10 days. The illness of this twin ran a more benign course than in C.F. During the first few days in hospital signs of meningeal irritation developed; there were some brief episodes of twitching and also several mild cyanotic attacks, but bottle-feeding was possible throughout. The second and third courses of antibiotics were given because of recurrence of vomiting and irritability with increased numbers of pus cells in the cerebrospinal fluid although the causative organism was not cultured again. Subdural taps were negative four weeks after the onset of the illness. The present mental state of the child at the age of 4 months is difficult to assess but the general impression is unfavourable; he holds his head up with difficulty and is taking little notice of his environment.

Bacteriological Investigation

When it was found that the meningeal infection in the first case was due to an intestinal type of non-lactose fermenting organism, the faeces of the patient were examined and a similar organism was isolated. The strains obtained from the cerebrospinal fluid and from the faeces were next subjected to detailed fermentation and biochemical tests but no serological tests were carried out at this time. When the second and third cases of meningitis occurred some seven weeks later in patients from the same hospital the strains isolated from the cerebrospinal fluids and faeces were again tested for their full fermentation and biochemical activities. The reactions of the three strains isolated from the cerebrospinal fluids are given in Table 1. Similar tests applied

TABLE 1
BIOCHEMICAL AND FERMENTATION REACTIONS

	Cerebrospinal Fluid Strains					
	24 hours			14 days		
	KL	CF	RF	KL	CF	RF
Adonitol	AG	AG	AG	AG	AG	AG
Dulcitol	O	O	O	O	O	O
Sorbitol	AG	AG	AG	AG	AG	AG
Arabinose	AG	AG	AG	AG	AG	AG
Xylose	AG	AG	AG	AG	AG	AG
Rhamnose	AG	AG	AG	AG	AG	AG
Maltose	AG	AG	AG	AG	AG	AG
Salicin	O	O	O	AG	AG	AG
Inositol	O	SA	SA	AS/G	AS/G	AS/G
Lactose	O	O	O	O	O	O
Sucrose	O	O	O	O	O	O
Mannitol	AG	AG	AG	AG	AG	AG
Glucose	AG	AG	AG	AG	AG	AG
Indole	+++	+++	+++	–	–	–
H_2S (7 days)	+	+	+	–	–	–
Gelatin	O	O	O	O	O	O
Koser's citrate	++	++	++	+++	+++	+++
Voges-Proskauer (48 hours)	O	O	O	–	–	–
Methyl-red (48 hours)	+++	+++	+++	–	–	–
Urea agar	O	O	O	+++	+++	+++
KCN (4 days)	O	O	O	–	–	–
Motility	+++	+++	+++	–	–	–

AG = acid and gas. O = no change. SA = slight acidity.
AS/G = acid with small amount of gas. – = not tested.

to the strains isolated from the faeces gave the same results. The cultural and biochemical characteristics of the various strains were not identical with those usually associated with typical strains of *Esch. coli.* They differed in that they fermented adonitol, produced acid and a slight amount of gas in inositol, grew in Koser's citrate medium, produced H_2S, utilized urea after a period of delay and failed to ferment lactose. The strains from the cerebrospinal fluid and faeces of the first case were submitted to Dr. P. R. Edwards and Dr. Ewing of the

TABLE 2
DETAILS OF TESTS OF THREE CEREBROSPINAL FLUID STRAINS

	Agglutination of Strains			Absorption of Sera		
	KL	CF	RF	KL	CF	RF
	'H' agglutination			*Titre after 'H' absorption*		
Serum KL 'H'	6·400	6·400	6·400	<100	<100	<100
Serum CF 'H'	12·800	12·800	12·800	<100	<100	<100
	'O' agglutination			*Titre after 'O' absorption*		
Serum KL 'O'	1·600	1·600	1·600	<100	<100	<100
Serum CF 'O'	800	800	800	<100	<100	<100

Enteric Disease Centre, Chamblee, Georgia, who reported that the organisms resembled *Esch. coli* more closely than any other type but were not related to the serological types of *Esch. coli* 1-137. They were, therefore, classified as intermediate coliforms. Since the cultural and fermentation reactions of all three cerebrospinal fluid and all three faecal strains were identical, 'H' and 'O' antigens were prepared from the K.L. and C.F. cerebrospinal fluid strains, and four rabbits were immunized. When the agglutinin titre in each animal's serum was sufficiently high, it was bled and the serum preserved with 50% glycerine. When all four sera were collected, agglutination and agglutinin absorption tests were carried out with the respective 'H' and 'O' antigens of all three strains isolated from the cerebrospinal fluid and of all three strains isolated from the faeces. The details of the tests for the three cerebrospinal fluid strains are given in Table 2 and show that they are serologically identical. As the strains obtained from the faeces gave similar serological reactions, these results are omitted.

As stated above, Ewing could find no serological relationship with any of the *Esch. coli* types 1-137. Further tests with polyvalent Salmonella and dysentery sera also failed to show any relationship with these groups of organisms. As a further confirmation of the identity of the strains isolated from the cerebrospinal fluids, their sensitivity to various antibiotics was examined. The method employed was to use the Sentest antibiotic discs prepared by Evans Medical Products, each antibiotic with the exception of bacitracin being tested in two concentrations. The results were recorded according to the approximate degree of inhibition and are given in Table 3. All three strains reacted in a more or less similar manner to 11 antibiotics, being most sensitive to chloramphenicol, neomycin and streptomycin, and less sensitive to the tetracyclines. They were insensitive to erythromycin, novobiocin, oleandomycin and penicillin.

After the second and third cases had occurred the question of the method of spread was considered. Accordingly specimens of faeces were obtained on two occasions from five nurses, four ward maids and two mothers, one being the mother of the affected twins. The nurses and maids might have had contact with the first case as well as the second and third, but the mothers could have had no contact with the first infection which occurred. None of the specimens showed the non-lactose fermenting organism so the actual source of infection was not determined. Furthermore, since the incidents occurred, all non-lactose fermenting and indole positive organisms isolated from specimens of faeces have been tested serologically with the sera prepared, but no further strains have been encountered.

Discussion

The organism isolated from the three cases was an unusual cause of meningitis. It was a non-lactose fermenting type which had fermentation and biochemical characteristics suggesting a variant of *Esch. coli*. The fact that it did not ferment lactose enabled it to be isolated from the faeces of the three cases as well as from the cerebrospinal fluids. Apparently it appears infrequently in faeces because, since the incident, some 1,500 specimens of faeces submitted for routine bacteriological investigation

TABLE 3
SENSITIVITY OF STRAINS TO TWO CONCENTRATIONS OF ANTIBIOTICS IN FORM OF SENTESTS

Antibiotic	Strains and Results (1)				(2)			
	Concentration	KL	CF	RF	Concentration	KL	CF	RF
Aureomycin	10 µg.	+	+	+	100 µg.	++	++	++
Bacitracin	100 µg.	—	—	—	—			
Chloramphenicol	40 µg.	+++	+++	+++	100 µg.	+++	+++	+++
Erythromycin	1 µg.	—	—	—	10 µg.	—	—	—
Neomycin	10 µg.	+++	+++	+++	100 µg.	+++	+++	+++
Novobiocin	2 µg.	—	—	—	10 ?g.	—	—	—
Oleandomycin	2 µg.	—	—	—	20 µg.	—	—	—
Penicillin	0·5 I.U.	—	—	—	2·5 I.U.	—	—	—
Streptomycin	20 µg.	+++	+++	+++	80 µg.	+++	+++	+++
Terramycin	10 µg.	+	+	+	100 µg.	+++	+++	+++
Tetracylines	10 µg.	+	+	+	100 µg.	++	++	++

have failed to show its presence. Presumably the organism must have been distributed through the agency of a carrier, for practically a month elapsed between the occurrence of the first case and the second and third. The investigation for such a carrier, however, gave entirely negative results. Presumably also the infants ingested the infecting organism, then developed a bacteraemia, and a subsequent meningitis.

Among the many types of Salmonellae a comparatively small number have been found to be responsible for most cases of spread to the meninges. The same may well be true of other members of the enterobacteriaceae although proof of this is at present lacking. In the majority of reports of this condition the organism is recorded as *Esch. coli* or paracolon bacillus without details of fermentation or serological reactions. Complete bacteriological data should if possible be given in future reports of such cases so that an answer can be found to this problem.

Summary

Three cases are recorded of neonatal meningitis occurring in a maternity hospital and due to a previously unidentified non-lactose fermenting member of the enterobacteriaceae.

We are grateful to Professor John Craig for permission to publish these cases, to Dr. N. S. Clark for advice and criticism, and to Dr. A. Sutherland for information and laboratory specimens from the maternity unit involved.

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NEONATAL PERFORATION OF THE COLON

BY

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Case History

Paul R., a male infant, aged 5 days, was born in hospital; his birth weight was 7 lb. 5 oz. The mother's pregnancy and the delivery were normal. Vomiting began immediately after birth and became increasingly severe. Scanty amounts of meconium were passed on the first, second and fourth days. The abdomen was said to have been protuberant as early as on the first day, and was referred to as distended on the third day of life.

The infant was seen by a paediatrician on the fifth day, who reported that he looked ill and dehydrated with balloon-like abdominal distension. Bowel sounds were present. On rectal examination a tight, narrow rectal orifice was found; there was meconium on the fingerstall. No other abnormal physical signs were detected. A radiograph of the abdomen showed that free air was present.

Progress. The child was given parenteral fluids and laparotomy was carried out. Free fluids and faeces were found in the peritoneal cavity, and there was a perforation in the transverse colon. The peritoneal cavity was cleaned out, and the transverse colon exteriorized at the site of the perforation in the form of a colostomy. The patient did not stand the operation well; he collapsed on the table and was resuscitated with difficulty. He was cold, pale and cyanosed on returning to the ward. In spite of appropriate treatment with intravenous fluids and oxygen his condition improved but little, and he died quietly 10 hours after the operation and 6 days after birth.

Necropsy confirmed the presence of a solitary perforation, 0·8 cm. in diameter, in the transverse colon, 11 cm. from the ileo-caecal valve. There was uniform dilatation of the whole of the large bowel right down to the anus. No thickened plugs of meconium were found. The peritoneum was deeply congested, with numerous scattered yellow meconium flecks. The remainder of the examination revealed no abnormality. Thus there was no evidence of meconium ileus, fibrocystic disease of the pancreas, Hirschsprung's disease or intestinal obstruction.

Discussion

Spontaneous perforation of the bowel in the newborn with peritonitis is barely mentioned in any of the standard textbooks of paediatrics. It is known to occur not only as a complication of meconium ileus and other forms of obstruction, but also in the apparent absence of any recognizable pathological lesion, when its aetiology may be quite obscure (Franklin and Hosford, 1952). Numerous factors have been implicated at different times (Thelander, 1939). Some of these have been largely of a conjectural nature, such as birth trauma, intra-uterine infection and interference with the blood supply to the bowel. Zachary (1957) in a small series of cases attributes perforation to pressure by hard plugs of meconium. In a few instances definite congenital defects of the muscle coats of the bowel have been found. Rudnew (1915) studied a case of foetal peritonitis due to perforation of the transverse colon. He found that the continuity of the muscularis mucosa was broken at frequent intervals by blood vessels and nerves surrounded by areolar tissue. The breaks in the muscularis were of considerable size, so that the mucous membrane could herniate through them. Fischer (1928) reported a case with two perforations of the colon. Examination of the areas adjacent to the perforations showed the absence of the circular and the longitudinal muscle layers. There was herniation outwards through one of the perforations of the mucosa and the muscularis mucosa. Boikan (1930) described excessive development of the lymphatic tissues and deeply penetrating crypts of Lieberkühn at the site of a neonatal colonic perforation.

Fig. 1 shows a section of the colon close to the perforation of the present case, described above. The most striking histological feature is the presence of a large number of dilated blood vessels throughout the wall of the gut. These almost replace the muscularis mucosa and interrupt at frequent intervals the circular and longitudinal muscle layers, which are scanty and ill-defined. It seems therefore that an area of weakness may have been created by this localized infiltration of the bowel wall with haemangiomatous material.

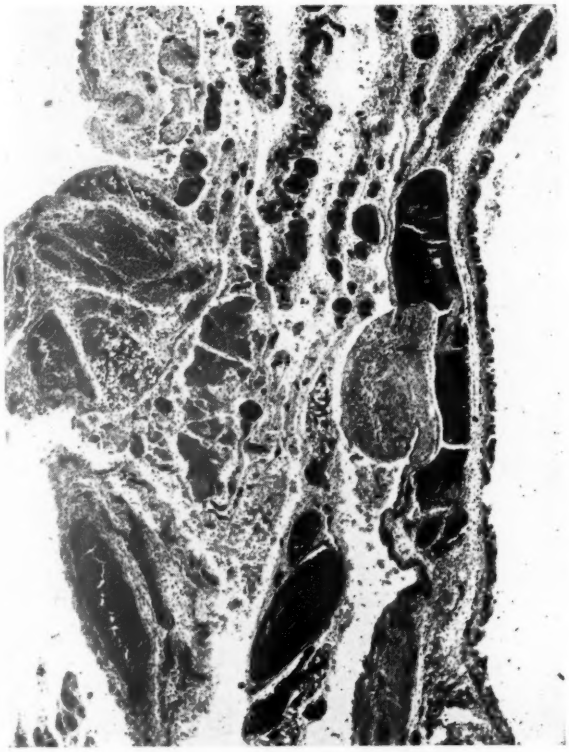

FIG. 1.—Section through colon near perforation showing haemangiomatous dilatation of vessels throughout wall.

This particular type of abnormality associated with spontaneous perforation of the intestine in the newborn does not appear to have been previously described. It is interesting, however, to compare it with the other congenital lesions reviewed above, which also weaken the muscular layers of the intestinal wall and so predispose to perforation.

Summary

A case of spontaneous perforation of the colon in a newborn infant is described.

A necropsy showed a solitary perforation and generalized peritonitis.

Histological section revealed a localized haemangiomatous abnormality at the site of the perforation, a lesion apparently not previously described.

I am indebted to Dr. K. H. Tallerman for his permission to publish this case, and for his help and encouragement. My thanks are also due to Mr. E. C. Butler, and to Dr. R. F. Parker who performed all the pathological examinations.

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BILATERAL PULMONARY AGENESIS

BY

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(RECEIVED FOR PUBLICATION DECEMBER 6, 1957)

Absence of one lung is an unusual malformation and has been the subject of an extensive review by Smart (1946) who was able to trace 33 cases of complete absence of one lung. A much more rare anomaly is complete absence of both lungs. Only three cases appear to be recorded in the literature. The first was reported by Schmit (1893) from Germany and the others by Allen and Affelbach (1925) and by Tuynman and Gardner (1952) from America. The following report appears to be the first of its kind from this country.

Case Report

The mother was a healthy primigravida aged 18 years. Apart from the usual childhood illnesses, including measles, she had been well up to the time of her pregnancy. She had no illness during pregnancy. The estimated date of delivery was May 2, 1957. When first seen on November 24, 1956, she was 18 weeks pregnant. She was Group A, Rhesus positive and the Wassermann reaction was negative. The pregnancy continued normally and labour began spontaneously at term on May 3, 1957. She was then admitted to hospital following an antepartum haemorrhage of about 100 ml. of blood. She was delivered of a male infant on May 4, 1957, following slight further blood loss.

The infant's colour was good at birth, it made several attempts at respiration and was said to have 'breathed'. A few minutes after delivery it was noted to be pale and limp. Resuscitation was attempted but was unsuccessful and heart sounds ceased 15 minutes after delivery.

Necropsy. At necropsy on May 5 the body was that of a rather small male infant weighing 2,500 g. and measuring 48 cm. in length. No congenital abnormality was found on external examination.

The falx and tentorium were intact. The brain was firm and no lesion was found on slicing.

When the thorax was opened the heart was seen to be occupying the right half of the thorax. The left side of the chest was occupied by a large thymus. Petechial haemorrhages were present in the parietal pleura and pericardium. There was no lung tissue visible and no bronchial structure was seen. The trachea was identified and was removed together with the larynx. It was noted that the trachea ended blindly (Fig. 1) and there was no

FIG. 1.—Anterior and lateral view of trachea showing rounded lower end and absence of bronchial buds. The intact oesophagus lies posteriorly. The pulmonary trunk, without branching, enters the aorta which is narrow proximally. A marker is inserted into the thoracic aorta.

evidence of an attempt at the formation of bronchial buds. The trachea measured 1·7 cm. in length and 0·5 cm. in diameter and only two poorly formed cartilagenous rings were found. It was uniform in size throughout its length and had a round end. The larynx was apparently normal. The mucosa lining the larynx and trachea was yellowish in colour.

The heart was of the expected size. There was anomalous venous drainage with a left superior vena cava opening into the left atrium (Fig. 2). The right

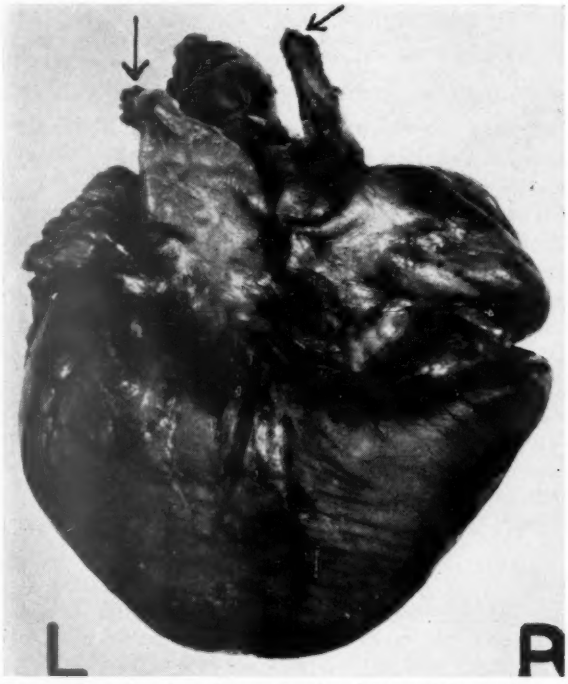

FIG. 2.—Posterior view of heart showing right and left superior vena cava (arrowed). Note absence of pulmonary veins.

superior vena cava and the inferior vena cava opened into the right atrium in the usual way. There was a defect in the inter-atrial septum. The tricuspid valve had a normal appearance. The pulmonary valve was also normal. The pulmonary trunk was of the usual calibre and 2·8 cm. above the pulmonary valve it joined the aorta distal to the point of origin of the left subclavian artery. There were no pulmonary arteries. The interventricular septum was intact. The aortic and mitral valves had a normal appearance. The left atrium was rather small and there were no pulmonary veins. The chamber received the left superior vena cava.

The aorta arose in the usual manner and the coronary arteries had a normal appearance. The aortic arch was directed to the left and the descending thoracic aorta showed no abnormality. There were no bronchial arteries. The arch of the aorta was abnormal. Coarctation was present for a distance of 1 cm. between the origin of the innominate artery and the point where the pulmonary trunk entered. In the narrow segment of the arch the aorta was just under half the diameter of the proximal portion. The oesophagus was intact and of the usual calibre.

The peritoneum was healthy and no lesions were present in the stomach or bowel. There was no transposition of the abdominal organs. The liver was of the expected size and no lesion was found on slicing. The diaphragm reached the level of the fourth interspace on each side. The spleen and lymph nodes were normal. There was no abnormality in the genito-urinary tract.

An anatomical diagnosis of bilateral pulmonary agenesis was made. There was congenital malformation of the heart with anomalous left superior vena cava and inter-atrial septal defect; absence of the right and left pulmonary arteries (the pulmonary trunk continuing straight into the aorta); and coarctation of the aorta.

Discussion

Complete absence of both lungs is of course incompatible with life and is thus of much less clinical importance than absence of one lung. Nevertheless, it is interesting to note that an attempt at respiration was made in all cases so far reported. It thus seems certain that the initiation of respiratory movement does not depend on the presence of lung tissue. Additional malformations in our case were confined to the heart. In the case reported by Schmit (1893) the trachea was connected with the oesophagus and there was a bony abnormality in the neck. The infant described by Tuynman and Gardner (1952) had an accessory spleen. Our case also differs from that of Allen and Affelbach (1925) in that the trachea ended abruptly, but in their case and in the one reported by Tuynman and Gardner, primitive bronchial buds were present.

The cardiac malformations are also slightly different in all three cases. The pulmonary artery joined the aorta at the point where the aorta and ductus arteriosus normally meet in all the cases. The left auricle received no vessels at all in the cases of Schmit and of Allen and Affelbach. In our case an anomalous superior vena cava entered this chamber and in the case reported by Tuynman and Gardner the inferior vena cava drained into it. In their case also, the aortic arch was directed to the right, a change which was absent in the others. A patent foramen ovale was reported by Schmit and by Allen and Affelbach and in our case the inter-atrial septum was deficient. Our specimen was also unique in showing a coarctation of the aorta.

According to Arey (1940) primary bronchial budding occurs at the 4 mm. stage of the embryo, i.e. at about the fourth week of pregnancy. It would appear, therefore, that the further development of the respiratory tract was interrupted just prior to this. The abnormalities in the heart and

great vessels are presumably the consequence of the failure of pulmonary development. Ellis (1917), however, has suggested that vascular anomalies may be the primary lesion. This does not appear to be likely in the present case as the development of the heart commences at about the 4 mm. stage.

Severe congenital malformations are known to follow certain virus infections in the mother, notably rubella. There was no history of any such infection in the present case. It is possible that the pulmonary and cardiovascular anomalies were genetically determined but the actual cause of the defect, as with most other congenital abnormalities, remains obscure.

Summary

A case of bilateral pulmonary agenesis in an infant born at term is reported. In addition to absence of both lungs there were a number of cardiac abnormalities, including an anomalous left superior vena cava and an inter-atrial septal defect.

We are indebted to Mr. E. Clark of the Bernhard Baron Memorial Research Laboratories, Queen Charlotte's Maternity Hospital, London, for the photographs.

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ATRESIA OF THE OESOPHAGUS WITH COMMON TRACHEO-OESOPHAGEAL TUBE

BY

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The clinical picture and anatomical variants of oesophageal atresia are well known now that this condition can be treated surgically with fair hope of success. In about 90% of cases there is a fistula connecting the lower segment of the oesophagus to the trachea and in some 9% the atresia is present alone without a fistula. Amongst the remainder there are instances where the fistula passes from the upper pouch to the trachea, where there is a fistula connecting each segment to the trachea and where a fistula occurs without any atresia (Waterston, 1954). In the case of the infant described here, however, though in life the findings did not appear out of the ordinary, autopsy revealed a most unusual malformation and it is perhaps fortunate that the child's general condition precluded any attempt at surgical correction.

Case History

A male child, birth weight 6 lb., was born rapidly at home five weeks before term. The pregnancy had been uneventful and he was the third child of healthy parents, the mother's age being 23. Respiration could not be established and atresia of the oesophagus became apparent when a catheter could not be passed into the stomach. Intermittent gasping respiration followed mouth-to-mouth insufflation and the child was transferred to hospital where, following intra-tracheal oxygen, a more regular, but stertorous and rattling, respiration was established about two and a half hours after birth. The child remained limp and unresponsive, with intermittent cyanotic attacks and a low temperature. Numerous rales were audible all over the chest and the intestines filled with air. After some hours the intra-tracheal tube was removed but, as the child's condition and colour promptly deteriorated, it was reinserted, this time rather further than before. It was then noted that the condition remained poor until the tube was withdrawn a short way, but the significance of this was not appreciated until autopsy. After 36 hours, during which time the child never developed muscle tone or became responsive, the stertorous respirations became periodic and death followed at 48 hours.

At autopsy an oedematous and congested brain was found with blood clot around the circle of Willis and brain stem. No aneurysm or bleeding point could be identified. The right kidney and all its ureter, apart from a short distal portion, were absent. The heart was normal and there were no abnormal blood vessels apparent in the neck and chest. The oesophagus ended blindly as a pouch 1 cm. below the laryngeal entrance.

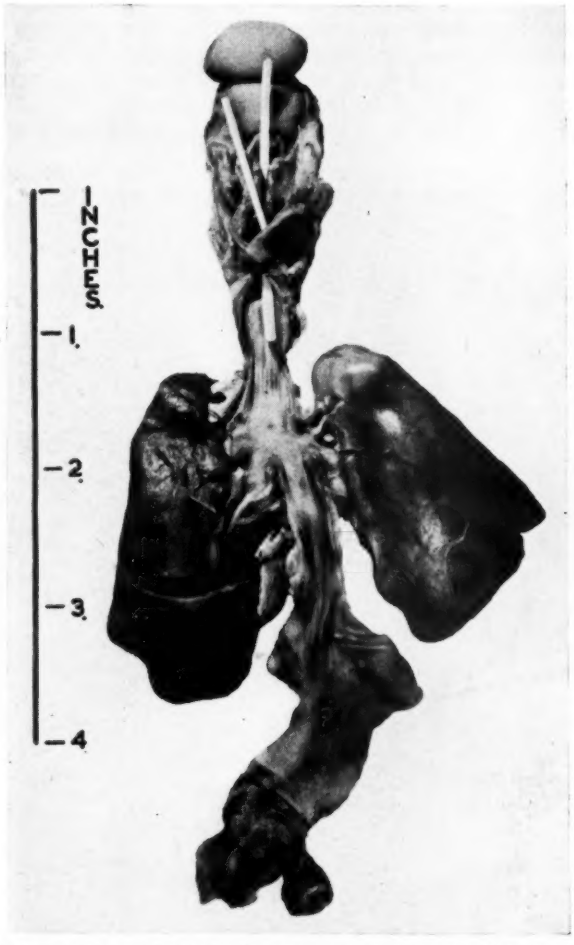

FIG. 1.—One marker lies under the oesophageal pouch and the other is passed through the larynx into the common tube.

The larynx was normal and opened wholly into a tube which appeared to be an oesophagus, but at its upper end, below the thyroid cartilage, were a normal cricoid cartilage and three poorly formed tracheal rings, all hidden behind the thyroid gland. The tube, having given off the two main bronchi in mid-thorax, passed normally through the left side of the diaphragm and into the stomach (Fig. 1). The bronchi and lobes of the lung were anatomically normal with well-formed cartilagenous rings.

Microscopy disclosed that the upper oesophageal pouch was lined by stratified squamous epithelium. There were no mucous glands and the submucosa contained a scanty muscularis mucosa. The wall was of striated muscle fibres arranged normally in outer circular and inner longitudinal coats (Fig. 2). The wall of the common tracheo-oesophageal tube contained only unstriped muscle fibres, mainly in longitudinal bundles with less well-developed outer circular fibres. The mucous glands were scattered generally throughout the submucosa, both superficial and deep, to the scanty and ill-defined muscularis mucosa, and also deep within the muscle coat. These glands had the appearance of those found in the normal trachea (Fig. 3). The epithelium gradually changed from stratified squamous above to a stratified cilated columnar form of the respiratory type near the origin of the bronchi and this passed gradually to the true respiratory mucosa in the bronchi themselves. Some of the mucosal epithelium had been stripped off by a mild inflammatory reaction and trauma (probably by the intra-tracheal tube).

The lungs were surprisingly well aerated with some scattered intra-alveolar haemorrhages.

Discussion

The interest of this case lies not only in the most unusual gross findings at autopsy but also in the histological appearance of this common tracheo-oesophageal tube which, though lacking all but the first three cartilagenous rings, had in it mucous glands of the type normally found in the trachea, as well as epithelium of both sorts. There is, of course, a wide variety of congenital anomalies involving trachea and oesophagus ranging from complete absence of the oesophagus (Wilkins, 1938) on the one hand, through absence of a segment of oesophagus (usually in association with a tracheo-oesophageal fistula), tracheal stenosis and hypoplasia (Wolman, 1941), to complete absence of trachea on the other. For two structures so intimately related in their development, it is surprising that the atresias of the oesophagus should be so much the more common. Estimates of its frequency vary, but it is probably in

FIG. 2.—Section through wall of upper oesophageal pouch. ×70.

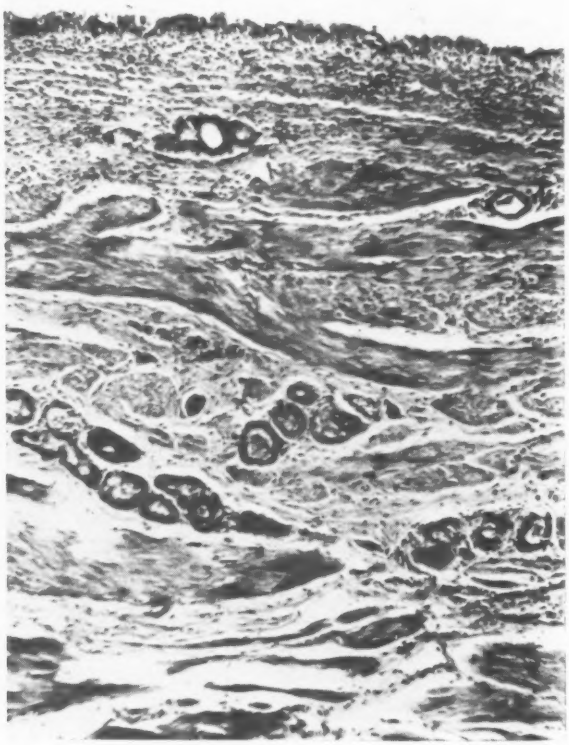

FIG. 3.—Section through wall of common tracheo-oesophageal tube, midway between larynx and bronchi. ×70.

he nature of 1 to every 1,500 births (Scott and Wilson, 1957). On the other hand, recorded examples of absence of the trachea are very rare. Fritz (1933) and Sandison (1955) have each reported a case where the bronchi opened normally into a short lower segment of trachea from the roof of which a fistula passed to a normal oesophagus. In the infants described by Kessel and Smith (1953) and Hempel (1956) the conjoined bronchi connected by a fistula to the oesophagus whilst in those recorded by Walcher (1928), Benešová and Peter (1934) and Marek (1940) the bronchi opened directly into the oesophagus. In Payne's case (1900) the main bronchi were connected to each other but to nowhere else, a state of affairs very similar to that described by Milles and Dorsey (1950). The continental authors mention a few similar cases in the earlier European literature, but the total numbers are few and in all the larynx is occluded by a sheet of cartilage or membrane with the oesophagus apparently otherwise normal, though without histological examination for the most part.

This wide range of abnormality indicates a developmental defect at a very early stage. Gruenwald (1940) has described the early stage of an oesophageal atresia and tracheo-oesophageal fistula in a 9 mm. embryo (5 to 6 weeks' ovulation age) and Ingalls and Prindle (1949) mention earlier reports of the fully developed malformation in 18·1 and 19 mm. embryos.

Normal Development. According to Frazer (1953) the first trace of the future respiratory system is apparent in the 2·9 mm. embryo (ovulation age 26 days) as a sagittal slit in the posterior part of the floor of the primitive pharynx, just cephalad to the oesophagus. This pulmonary outgrowth appears externally as a keel-like projection which soon begins to extend caudally over the ventral surface of the oesophagus, the two lung buds appearing at its lower end. By the 4 mm. stage the entodermal lung buds are projecting into a mesodermal mass continuous at its caudal end with the septum transversum which, being fixed, serves to anchor the lung buds in their subsequent development. Lateral ridges appear in the pulmonary outgrowth and fuse mesially in a caudo-cephalic direction at the same time as the oesophagus and pulmonary outgrowth are elongating rapidly, thus separating progressively the primitive main bronchi, trachea and infra-glottic part of the larynx from the oesophagus. When the pulmonary outgrowth first appears only the first two pharyngeal arches are apparent, but by the 5 mm. stage (30 days) it has come to lie between the sixth arches, just behind the hypobranchial eminence. The major (supraglottic) part of the larynx, down to and including the vocal cords and the cricoid, develops from the fourth and sixth arches and the hypobranchial eminence and is thus pharyngeal in origin, which perhaps explains why the larynx is more or less normal despite absence of the trachea beyond in the cases mentioned. In its early stages the narrow infraglottic cavity is compressed from side to side and is almost completely occluded for a short time by epithelial fusion, only small dorsal and ventral tracts leading to the patent part of the tracheal outgrowth. The larynx is well seen in the 16 mm. embryo (about the seventh week). Early in its development the cells lining the oesophagus undergo intensive proliferation but vacuoles become apparent at the end of the sixth week and, although occlusion occurs as a temporary phase in the crocodilia and reptiles (Reese, 1926), it is never complete in the human (Johns, 1952). Chondrification in the trachea becomes apparent at the 20 mm. stage.

The associated absence of kidney also helps to date development of the abnormality as the ureteric bud appears at the end of the fifth week. Rosenthal (1931), Ladd (1944) and Sandison (1955) have also recorded instances where absence of kidney is associated with tracheo-oesophageal abnormalities.

Pathogenesis. Rosenthal (1931), amongst others, has reviewed the theories of pathogenesis of oesophageal atresia, and divides them into three main groups, those based firstly upon retardation of oesophageal development at a time when it is solid (subsequently shown to be a faulty premise), secondly upon deviations and malformations of the tracheo-oesophageal septum and thirdly upon the presumed effects of changes in tension on the developing embryo (as might be exerted by an overlarge cardiac anlage, excessive flexion of the embryo or the development of blood vessels in abnormal sites).

The defect seen in this case, however, appears to be far more fundamental with the persistence of a common tube. It can best be explained on the assumption that the lateral ridges have never appeared and the pulmonary outgrowth has thus never separated from the oesophagus. The lung buds have penetrated the mesenchyme in the usual manner and with the subsequent growth of the embryo, larynx and bronchi have become widely separated. The larynx, being pharyngeal in origin, has developed normally, as have the lung buds. The existence of the dorsal oesophageal pouch behind the larynx is explained by the fact that the upper portion of the oesophagus derives partly from the

pharynx (it contains striped muscle in its wall). The posterior wall of the pharynx, at the level of the pulmonary outgrowth, has formed the pouch, perhaps after the fashion of a pulsion diverticulum. Associated with this defect is a lack of chondrification of the majority of the tracheal rings.

Summary

Details are presented of an infant in whom an oesophageal atresia was found in association with a common tracheo-oesophageal tube from which arose bronchi and stomach. The pathogenesis of this and similar conditions is discussed.

Our thanks are due to Dr. B. D. R. Wilson for permission to publish details of this child and to Dr. H. Spencer and others for their help and advice.

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PSYCHOGENIC MEGACOLON IN CHILDREN: THE IMPLICATIONS OF BOWEL NEGATIVISM*

BY

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Introduction

The demonstration of a precise histopathological basis for Hirschsprung's disease (Whitehouse and Kernohan, 1948; Zuelzer and Wilson, 1948; Bodian, Stephens and Ward, 1949; Swenson, Neuhauser and Pickett, 1949; Hiatt, 1951; Lee and Bebb, 1951) has permitted a radical revision in our concepts regarding the aetiology and management of megacolon. The condition should be designated more accurately as congenital neurogenic or aganglionic megacolon. It is possible to differentiate this state from a more commonly occurring group of cases, also characterized by colonic enlargement, but in which no spastic, aganglionic segment or other organic lesion can be demonstrated. These cases have been designated as 'idiopathic' or functional megacolon (Bodian *et al.*, 1949). It is with this group that the present study is concerned.

Object of Study

Idiopathic megacolon has been attributed to a state of chronic colonic inertia (Bodian, 1952). The present investigation seeks to demonstrate, however, that megacolon can develop in children primarily on a basis of emotional factors. The condition so produced closely resembles idiopathic megacolon in clinical features and radiographic appearances. It is contended that the two entities are identical, and that, while colonic inertia forms the immediate basis of the disorder, its ultimate aetiology is psychogenic in nature.

The importance of this submission lies in the approach to treatment. It is claimed that sustained results are not procured in such cases from purely symptomatic measures of relief, and that a satisfactory long-term response is achieved only through adequate evaluation and correction of the relevant emotional factors which contribute to the condition.

* Abstracted from a thesis for the degree of M.D. awarded by the Faculty of Medicine, University of Edinburgh, 1956.

Case Material

Thirty cases are presented, 19 boys and 11 girls, ranging in age from 24 months to 15 years. In all of them there was a history of functional bowel disorder varying in duration from eight months to 15 years, and presenting mainly as chronic constipation, cumulative faecal retention and overflow soiling.

The series was collected over a period of three years. The chief sources of referral were consultant paediatricians and paediatric surgeons who had previously had the cases under treatment either as out-patients or in-patients. Investigation had shown no organic basis for the disorder, and the children were referred for psychiatric opinion either because of their unsatisfactory response to standard treatment measures or because the disorder was suspected to have an emotional basis. In those of the series investigated by barium enema, radiographic appearances confirmed the presence of functional megacolon.

For comparison, a series of control cases was constructed from the record of admissions to a general paediatric hospital over the five-year period, 1950 to 1955. Examples were sought of children of equivalent age range referred with a history of constipation which warranted investigation and treatment in hospital, but in whom no organic lesion was demonstrated and who had responded satisfactorily to routine treatment procedures without subsequent relapse. Twenty-one cases, 14 boys and 7 girls, were found to fulfil these criteria.

These cases were traced and followed up independently by a senior psychiatric social worker, who conducted her assessment on each case in parallel with the model adopted for the investigation of the primary series. In this way, unbiased comparison between the two groups was made possible.

The clinical material thus comprised 51 children, 30 of whom formed the primary series under study, and the remaining 21 the control group.

Statistical Analysis

Statistical analysis of comparable findings in these two groups is of limited value because of the small numbers involved, but, using a Chi-squared test with Yates' correction for small numbers, four significant differences between the primary and control groups are apparent. It seems reasonable to ascribe aetiological significance to each of these four factors, namely, (1) parental personality characterized by excessive rigidity and/or excessive anxiety; (2) primary coercive toilet training; (3) parental fears and prejudices relating to constipation; and (4) parental over-valuation of the child (Table I and Fig. 1).

Formulation

From the analysis of case material, compared with the findings of the control group, it is possible to construct the following formulation to explain the aetiology of psychogenic megacolon.

The primary mechanism involved, I suggest, is a state of negativism on the part of the child, expressed as persistent refusal to defaecate or, less frequently, as defiant soiling. If handled unwisely, this state may result in cumulative retention of faeces with progressive loading of the rectum and terminal colon and subsequent overflow faecal soiling. Ultimately, chronic dilatation of the distal bowel develops which is demonstrable radiographically. Confirmatory evidence of such negativistic trends in the children under study is provided in their clinical assessments.

It is significant that with one exception in the primary series, this negativistic pattern developed during the first three years of life. As such, it coincides with the period of resistance (Kanner, 1948), or the phase of defiance (Menninger, 1943), undergone by most children at the stage in their emotional development when they become aware of their independence from the mother as a separate personality. During this period, provocative and testing behaviour towards parents is common, and bowel negativism is one of the acknowledged forms which such behaviour may take.

Indeed, it is recognized as so universal a pattern that in itself it could hardly represent the entire psychogenesis of the bowel disorder. Moreover, the onset of constipation in the control group also coincided, more or less, with the period of resistance through which some of these control group children might be assumed to be passing. Yet negativism in these latter cases, where it existed, did not give rise to a degree of bowel disorder commensurate with what was found in the primary series. Clearly, therefore, additional factors must operate to bring about the differential response between the primary and control groups.

It is contended that anal negativism forms the basis of the disorder, but that it is aggravated, or intensified, by specific conditioning factors operative in the primary series to a significantly greater degree

TABLE 1
CASE FINDINGS IN PRIMARY SERIES AND CONTROL GROUP

	Primary Series (30)	Control Group (21)
Age at onset of symptoms (years):	Less than 1 12 1-3 17	8 13
Sex distribution:	Male 19 Female 11	14 7
Clinical features:	Chronic constipation 25 Pseudo-diarrhoea 5	Abdominal colic, constipation with or without vomiting: 18 Constipation: 3
Radiographic findings:	Considerable dilatation of rectum, pelvic and descending colon, often with redundancy of pelvic loops	Normal
Response to treatment with laxatives, enemata:	Of temporary benefit only	Satisfactory
Parental personality:	Perfectionist, strict or domineering: 19 Overanxious, emotionally tense: 9	Normal
History of coercive toilet training:	17	None
Parental fears of constipation:	22	1
Parental over-valuation of child:	18	2
Negativism in child:	30	5

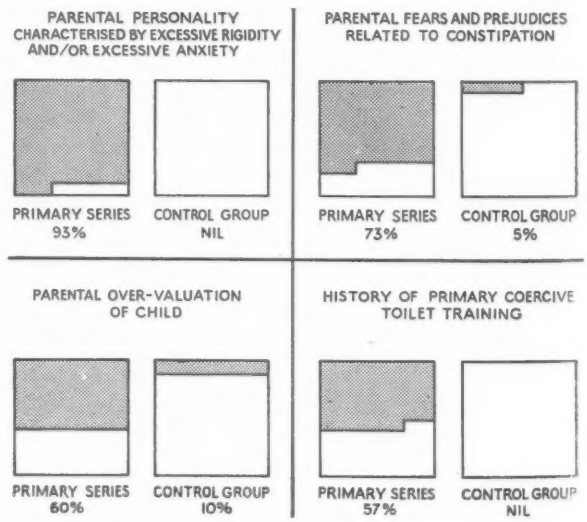

FIG. 1.—Statistically significant differences between primary and and control groups.

than they are in the control group. Given a basis of bowel negativism, it is the operation of these contributory factors, sufficiently intensely or for a long enough period, which converts the case into one of psychogenic megacolon. These factors can be classified as predisposing, precipitating and perpetuating.

Predisposing Parental Personality. The two main personality variants found among the parents of the primary series are, first, the perfectionist, rigidly obsessional parent who seeks to train the child by coercive methods to acquire bowel control at a premature stage in his development, in advance of adequate neuro-muscular maturation; and, secondly, the over-anxious, over-solicitous parent whose general attitude to the child is fraught with tension, and who closely supervises bowel evacuation because of her fears for the child's well-being.

Predisposing Parental Prejudices and Misconceptions. Linked to these emotional patterns in the parent are certain ingrained misconceptions with which the act of defaecation is still widely invested. These in turn give rise to various fears concerning the allegedly harmful effects of constipation. The over-anxious parent is specially prone to such fears.

Equally widespread is the notion of filth which invests the faeces once they are evacuated. The obsessional and fastidious type of parent is most prone to experience a sense of obnoxiousness regarding the stool, and to imbue the child with an irrational feeling of disgust or shame towards a perfectly natural product of excretion.

Thus we have the combination of personality type and parental attitude to defaecation, which accounts for much of the pressure to which these children are subjected in attempts to promote their regular bowel function.

Predisposing Environmental Factors. Particular circumstances surrounding the life situation of the child may conspire to generate excessive tension in the parents' attitude towards him and may provide the motive for excessive attention to his bodily functions. In the main, the factor involved is emotional over-valuation, which in turn contributes to excessive parental concern for the child.

Precipitating Stress Factors. Focal circumstances may provoke the immediate reaction of bowel difficulty against a background of any of the predisposing factors already discussed. There is, for example, fear of defaecation resulting from accidental fright during bowel action. While such events may induce temporary inhibition of stool, it is doubtful whether the effect ever persists and becomes chronic in the absence of predisposing factors which are already operating.

Similarly, although the disorder began as simple constipation due to intercurrent factors, in a number of the primary series it required the introduction of additional factors to elaborate the disorder into one of major bowel disturbance. It is highly significant that such a development did not take place in the control group, although each of these cases had an equivalent basis of simple constipation.

Perpetuating Factors. Excessive parental anxiety, alone or combined with excessive parental rigidity, will continue to operate if the child's initial response to treatment is unsatisfactory. In these circumstances, persisting parental tension will act as a perpetuating factor.

Continuing constipation in itself may give rise to anal spasm, secondary anal fissure, rectal prolapse or peri-anal dermatitis, any of which may perpetuate the disorder through the resulting pain on defaecation.

Yet another perpetuating factor may be the child's own reaction of anxiety and guilt in face of the persisting symptoms, or in response to parental attitudes of censure or ostracism.

It is contended that the interaction of these several contributory factors is responsible initially for evoking the child's resistance in the sphere of bowel function, and for subsequently elaborating his negativistic response to the stage at which psychogenic megacolon develops.

This hypothesis was put to the test in evolving a programme of psychotherapeutic treatment for the condition.

Treatment

Preliminary Orientation of Parental Attitude. Treatment was first directed to convincing the parents that what they had formerly regarded as a physical disorder was in fact of emotional origin, and that, in consequence, it would be necessary to substitute psychological methods of treatment for the local treatment hitherto adopted.

Parental reactions to this approach ranged from frank incredulity, through hostile resistance by obsessional parents or increased concern by over-anxious parents, to simple failure on the part of intellectually limited mothers to appreciate the relationship at all. In the latter case an authoritative approach was the only course practicable.

One of the difficulties was the implication that the parents themselves were intimately involved in the child's pattern of reaction, and that, henceforth, treatment was to be directed away from the present-

ing symptoms and conducted predominantly through them. In two cases, the maternal anxiety aroused by this implication proved too great for acceptance and both patients were in fact withdrawn from further attendance.

Dispersal of Parental Fears and Prejudices. In every case, acute parental concern was felt about the potential danger to the child's physical health as a result of his bowel disorder. Parents of predominantly rigid personality were as much beset by these fears as parents who were primarily over-anxious.

The task of reassurance was hindered in the majority of cases by advice or instruction about the importance of bowel regularity previously tendered by district nurses, health visitors, child welfare clinic staff, hospital medical and nursing staff or by the family doctor. Commercial advertisements about laxatives and books dealing with child care had also inadvertently helped to augment parental fears.

To overcome this attitude, and to dispel these misgivings, certain procedures proved valuable. As far as possible, for example, parents were initially interviewed in joint consultation with a paediatrician in sympathy with the psychiatric approach. At these interviews unequivocal and authoritative reassurance was given. It was necessary to repeat it until no vestige of doubt or misgiving remained in the mind of the parent. Vague or generalized advice merely served to heighten the parental anxiety. It was important to stress that no organic disease or abnormality of the bowel was present, that there would be no harmful results from persistence of the constipation, that spontaneous bowel function would be restored despite the 'stretching' of the lower bowel, that the child's rectal sensation had not been irrevocably lost and that anal fissure, rectal bleeding and rectal prolapse were only temporary sequelae. It was also necessary to explain to the parents that the child's wriggling and contortions did not represent his difficulty in expelling the faeces, but, on the contrary, indicated his determined attempt to retain them.

Although necessary, such dogmatic reassurance was of no lasting value in itself, save in the case of parents who were limited in intellectual endowment. For the majority of parents it was imperative to determine by supplementary questions how much of the initial advice had been absorbed, and to reinforce repeatedly those points which had not previously been understood or accepted adequately. Such interpretative reassurance could not be emphasized enough, reiterated too often or confirmed too insistently to ensure that it had been genuinely credited by the parents.

The limitations and dangers of excessive purgation had also to be emphasized. It was explained that, at this stage, drastic purgatives would serve no useful purpose and might, indeed, further impair bowel function. They were also likely to increase the soiling. It was equally essential that the medical advice given should be consistent, and that, therefore, laxative therapy should be discontinued, otherwise parents reasoned that if no danger were anticipated from permitting the constipation to go on untreated, why the need for maintaining laxatives.

Winnicott (1953) has referred to the need for 'symptom tolerance' in child psychiatric cases which present with physical symptoms. There is an understandable tendency among paediatricians to treat and remove presenting symptoms by direct approach as early as possible in the course of the disorder; whereas the discipline of child psychiatry advocates the frequent need for toleration of symptoms while the basic treatment is directed at the underlying causative emotional factors. This differential attitude, derived from the difference in training between the paediatrician and child psychiatrist, is exemplified in the treatment approach to the present series of cases. There was a tendency among paediatricians to continue standard treatment measures parallel with psychotherapy, either to 'make quite sure' or through a desire to resolve the disorder more rapidly by utilizing both methods of treatment together. They were intolerant of the persistence of symptoms.

Such a practice, however, is exposed to two risks. First, the parents may misinterpret it, and regard it as evidence that the medical adviser himself lacks confidence in the policy of suspending physical and medicinal measures; parental confidence is correspondingly undermined. Secondly, the maintenance of standard treatment measures may convey to the child that the emotional investment in his symptoms has not been withdrawn, and his motive for persisting in negativistic behaviour may thus be given fresh impetus.

For these two reasons, I found it advisable to suspend standard treatment procedures, apart from ensuring an adequate fluid intake.

Promotion of Parental Insight. It was just as important to avoid premature explanation to the mother of the emotional dynamics of the child's disorder in advance of her preparedness to accept such explanation. The more effective policy in practice was to withhold interpretation until the parents had disclosed their own resistances and preconceived opinions so that these could first be dealt with.

Having first assured them that there was no physical basis to the disorder, suggestions were put to them along the following lines. If there was no organic reason to prevent the child opening his bowels, why did he continue to hold back? Clearly this policy was causing him discomfort and pain and therefore, presumably, he must be deriving some compensatory gain. What might his motive be?

By such provocative suggestions, parents were stimulated to enlarge their concept of the disorder to include the possibility of emotional motivation, and to appreciate how their child's behaviour could conceivably be directed against them.

It was explained to them in general terms that young children often tried to even out the unequal balance between their own puny power, and what appeared to them to be the overwhelming authority of their mother and father. They could not defy this authority directly with impunity, but they often sought to do so indirectly by becoming obstinate and contrary in any sphere of behaviour which they sensed might upset their parents. The more concern shown over this conduct, the more the child tended to persist with it. This was emphasized as an entirely normal and almost universal pattern of behaviour. Parents must not feel therefore that they were necessarily to blame because it was adopted by their child. They had simply made the mistake, it was explained to them, of continuing to register excessive concern which the child had been quick to sense.

Modification of Parental Attitudes. At this stage, parents were sufficiently receptive to cooperate in reversing their original attitudes to the child's bowel function. They were advised to practise complete indifference towards the persistence of symptoms. No further mention must be made of the need for bowel movement, and no censure must be shown towards continued soiling. This was a difficult assignment for the mother. It meant in effect a policy of ignoring the symptoms in place of her former policy of perhaps agitated exhortation. Only confidence in the therapist, and the knowledge that she would be absolved from responsibility should anything go wrong, made it possible for her to pursue this course.

A frequent sequel, however, was the transfer of the child's negativism to some alternative sphere of conduct. Deprived of the focus of parental concern over his bowel symptoms, he might first attempt to re-establish his position by intensifying his references to bowel activity. For example, several children resorted to repeated demands to be helped in their toilet procedure. They would follow their mother around the house, insisting that she flushed the toilet for them, or unfastened their trousers, or in some similar way supervised their act of defaecation. Parents were instructed in advance to ignore all such overtures and to adhere strictly to their attitude of disinterest.

Group Therapy with Parents. In the great majority of cases, therapy was conducted predominantly through the parents and chiefly through the mother. In the course of formulating the treatment approach in the present study, a scheme was evolved for treating mothers by group therapy. Group leaders were chosen from among those mothers who had achieved the greatest depth of insight, who expressed enthusiastic support for the psychiatric view-point, and who were endowed with adequate talents for disseminating the principles which they themselves had absorbed. Four mothers emerged from the series as best suited for this purpose and as willing to cooperate. Each in turn formed the nucleus of a group of eight mothers, the membership of which changed from time to time as earlier cases acquired insight and dropped out, to be replaced by new cases. The group leadership similarly changed as a new leader came forward.

Group meetings were convened at regular weekly intervals for periods of one and a half hours under the general chairmanship of the therapist. His role was to supervise and guide the discussion but to remain as far as possible unobtrusive. He sought to promote free interchange of views between the older and more recent members, prompted by the group leader.

Considerable support was derived by new members through introduction to the group. Each in turn was relieved to find other mothers in similar straits and having to cope with identical problems. The inevitable prejudices, doubts, resistances and fears, once expressed, were more readily resolved within the group, and the acquisition of insight more readily promoted. There were repeated examples of sceptical and insecure mothers showing greater willingness to accept reassurance and advice from the group leader, or from older members of the group, than from the therapist direct. The evidence of success achieved by the psychiatric approach in earlier cases, and now placed squarely before the new case, was a potent therapeutic instrument.

Direct Therapeutic Procedures with the Child: (*a*) Admission to Hospital. In nine cases, it proved necessary to admit or re-admit the child to hospital for varying periods, under the supervision of the therapist. This step was taken with four of the

children because the mother's response to reassurance had not been sustained, or because she was too limited in intellect to benefit from the guidance given without some more concrete demonstration of how to manage her child. In the remainder of this group, carping parental pressure or excessive domination of the child were most effectively curtailed by temporary removal of the patient from home.

In the absence of separate in-patient facilities, all nine cases were individually admitted to a general paediatric ward through the kind cooperation of my colleagues. The nursing staff were prompted to adopt an attitude of bland detachment towards the persistence of bowel symptoms, and equally to ignore any associated symptoms such as refusal to eat, temper tantrums, emotional withdrawal or provocative behaviour. The child was treated warmly and tolerantly but with avoidance of fuss.

In the majority of these cases no specific play therapy as such was practised with the child. Treatment essentially comprised placing the patient in a temporary residential environment, designed to counteract pre-existing influences and to achieve resolution of symptoms by engineering a suitable atmosphere. It was found that these children responded well to consistent and detached handling. In the main, they adjusted readily to ward routine, with restoration of spontaneity and regularity in bowel function after a short interval. Subsequent supportive treatment with the parents depended upon the practical example set by managing the child in hospital.

Apart from admission to hospital as a means of temporarily modifying the child's environment, direct psychotherapy was required in a further group of cases, including some who were accepted as in-patients. Such direct intervention was necessary with the child for a number of different reasons. It might be that the symptoms had become so chronic and entrenched that the child had developed an overlying bland façade which warranted definitive treatment measures. This was particularly so among the older children. Alternatively, some children were so grossly inhibited, fearful and insecure as to merit direct therapeutic help. Yet a further important indication for direct psychotherapy with the child was the unresponsive attitude of the parent, or the persistence of parental intolerance and rejection, with failure to acquire insight.

(*b*) **Play Therapy.** The aims of expressive play therapy were, first, to penetrate the child's defensive façade and establish adequate depth of contact with him; secondly, to define his fundamental problem for him through the medium of projective play techniques; thirdly, to promote the working-through of his difficulties, with associated release during play of his pent-up hostility; and, fourthly, to restore his emotional stability following the resolution of these difficulties.

Three main techniques were employed in this procedure: (*a*) the 'World Picture' technique, with portrayal of the child's own fantasy productions in a sand-tray as described by Lowenfeld (1939); (*b*) the technique of free drawing by the child on paper; (*c*) the combination of expressive drawing on paper with a device known as the aggression board. This latter technique will be described as exemplifying the treatment approach.

This apparatus was evolved by Meals and Summerskill (1951), as a technique for diverting hostility in children under treatment. It consists of a sheet of thin plywood (3 ft. by 4½ ft.), held in a thicker frame, and supported behind by a hinged brace which fits into a thick wooden base on the floor. In the plywood sheet, a square hole (8 in. by 8 in.) is cut out in the lower half. The base supports the plywood at an angle of 45°, facing the child, with the top of the board inclined away from him (Fig. 2).

In the present work, the apparatus was used by

FIG. 2.—The aggression board.

inviting the child to make a drawing on a large sheet of paper of something which he particularly disliked; no other limitation was imposed. The paper was then taped across the aperture in the plywood board so as to cover the hole. Facing the board, at a distance of four or five yards, the child was provided with 12 bean bags and encouraged to throw them, one after the other, at the picture over the opening. If he struck the target the taut paper was ripped by the impact. If he missed the drawing, the bean bag hit the surrounding plywood with a resounding noise which was obviously satisfying to the child.

The more inhibited of the children under therapy were unwilling to use the apparatus and showed fear of its aggressive potentialities. With the remaining cases, however, it proved both of diagnostic and therapeutic value. The subject matter drawn by the child as an object of his dislike provided diagnostic information, while his treatment of the drawing permitted therapeutic release of his aggressive feelings.

The following examples will suffice to indicate the type of material which emerged. Repeatedly the drawings referred to the administration of enemata by nurses as experienced by the child himself. The treatment meted out to these drawings left no doubt about the patient's hostile feelings.

Figure 3 shows a drawing undertaken by Case 9. Case 11 was more forthright in his portrayal of the same subject (Fig. 4). In this drawing, the nurse,

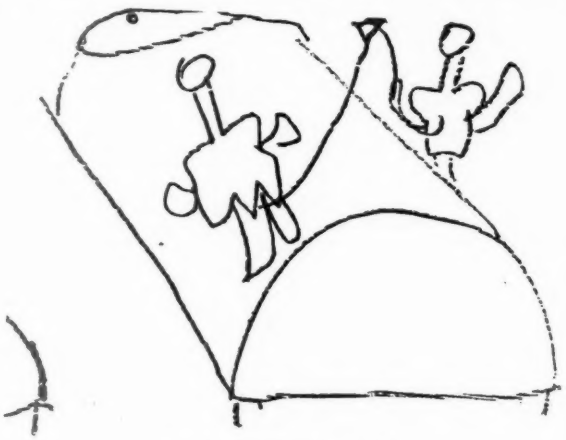

FIG. 3.—Drawing by Case 9.

menacing in appearance, is depicted as saying, 'I've never known anyone so rude, I'll give you another enema for that'. The child, though clearly sobbing, replies spiritedly, 'I'll give you an enema, you darn pest'. Treatment of this particular drawing was vigorously destructive with bean bags.

The same theme was repeated at a subsequent

FIG. 4.—Drawing by Case 11.

Nurse: 'I've never known anyone so rude, I'll give you another enema for that.'
Child: 'I'll give you an enema, you darn pest.'

session, during which the child threw handfuls of wet sand violently at the plywood board when he had exhausted the supply of bean bags. The actual scene is depicted in Fig. 5.

FIG. 5.—Aggression board with the drawing depicted in Fig. 6 in position.

FIG. 6.
Child: 'Boo-hoo, this hurts.'
Nurse: 'I'm sorry, but I have to do it.'
Child: 'I know, tomorrow I will call you Nursie.'

Nevertheless, the verbal exchange between nurse and child in this later version is more conciliatory. The nurse, who no longer looks fierce, is saying, 'I'm sorry, but I have to do it'. The child openly concedes his discomfort ('Boo-hoo, this hurts'), but acknowledges the nurse's overture by replying, 'I know, tomorrow I will call you Nursie'. (Fig. 6.) This conciliatory trend was actually reflected in the patient's increasing stabilization and in the reduced intensity of his provocative behaviour at home.

By contrast, although the same theme was portrayed among the more inhibited and insecure children, their treatment of the subject was significantly different. For example, Fig. 7 shows a nurse administering an enema to a child behind screens in hospital. This drawing was done by a withdrawn little girl who volunteered no comment, and the picture itself seemed devoid of animation.

FIG. 7.

A further example of the same subject is portrayed in Fig. 8. This picture is more animated and captions have been introduced. The patient is saying, 'I'll teach you old Nursie a lesson'. The nurse, wearing a frightening expression, replies, 'No, you won't, you can't'.

It is interesting to compare this drawing with that depicted in Fig. 4, which so obviously expresses spirited defiance. In Fig. 8 the protest by the child is clearly more feeble and is emphatically overruled by the all-powerful nurse. The difference in attitude expressed in these drawings reflected the clinical difference between the first patient, a boy who was reacting with robust retaliatory behaviour, and the second patient, a girl who was much more inhibited and passive in response.

FIG. 8.
Child: 'I'll teach you old Nursie a lesson.'
Nurse: 'No you won't, you can't.'

Results of Treatment

With the kind of treatment outlined above, remission of symptoms occurred in 21 cases in the series, 17 of whom have now received no active treatment for periods up to three and a half years. Three children still continuing treatment are showing increasing symptomatic improvement. Of the remaining six cases, three failed to maintain attendance for treatment, and three have proved unamenable to psychiatric treatment (Fig. 9).

Discussion

It is noteworthy that the present series showed a preponderance of boys to girls in the ratio of almost 2 to 1 (19 boys, 11 girls). In Bodian's (1949) original group of 34 cases of idiopathic megacolon, the corresponding numbers were 25 boys and 9 girls. Bakwin (1956) has commented that resistance to bowel training and the persistence of soiling is twice as common in boys as in girls. An explanation may lie in Freud's observation that

'the little girl is as a rule less aggressive, less defiant and less self-sufficient . . . The fact that she is more easily and more quickly taught to control her excretions is very probably only the result of this docility.' (Freud, 1946.)

In several cases of the primary series, there was a manifest tendency among the mothers to overvalue their sons relative to their daughters. This might conceivably provide the motive in some cases for the excessive focus of attention on bowel regularity in the male.

The personality characteristics which were found to predominate among the parents of the children in the present study have been noted by other workers in association with difficulties over toilet performance (Lehman, 1944; Comly, 1952). The personality features of obsessional rigidity, determination and perfectionism, which were so prominent in the parents concerned, correspond to the characteristics of the 'anal character' elaborated by Freud (1916).

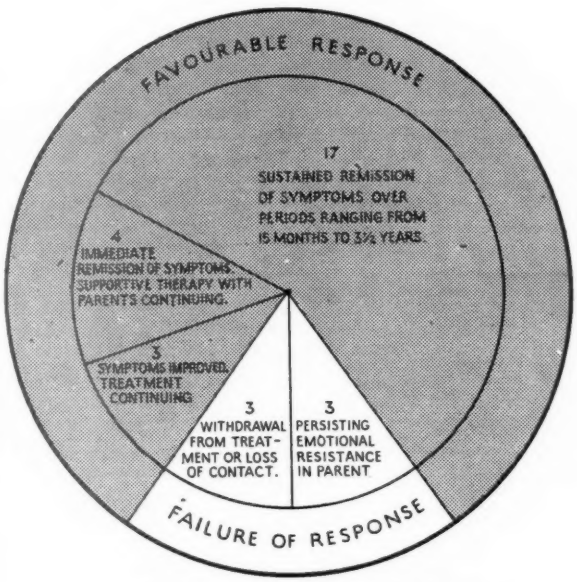

FIG. 9.—Response to treatment in the primary series.

A study of the family backgrounds of these parents yielded repeated evidence of the strict code of upbringing to which one or other parent, usually the mother, was herself subjected in her own childhood. It was significant that the parental attitude adopted toward the child was often in part determined by the parental attitude which had obtained in the previous generation.

The role of coercive toilet training in promoting bowel negativism has been stressed independently by different workers (Huschka, 1942; Swenson, 1953; Richmond *et al.*, 1954; Bakwin, 1956).

Prugh (1955) found that constipation, with or without faecal soiling, occurred twice as frequently in a group of children who had been subjected to early bowel training as in an equivalent group who had been trained at the usual time. He concluded, however, that it is not the timing or nature of bowel training which alone promotes difficulties over defaecation. In his experience, mothers who enjoy a warm and close relationship with their offspring can adopt premature or even coercive training without incurring any serious risk of subsequent bowel disorder. He adds, however, that 'if the relationship between mother and child is strained, undesirable procedures may offer a focus around which these tensions are expressed'. He therefore considers that 'the personality make-up of the mother, and her relationship to her child, are more important than her technique of toilet training'.

This view is borne out by the findings in the present series of cases, among whom 57% had been submitted to primary coercive training, whereas 93% showed evidence of parent/child tensions due to personality difficulties in the parents.

Paediatricians are alive to the fact that constipation is still widely invested by the lay public with ingrained fears and fantasies concerning its allegedly adverse effects. Accordingly, they recognize the importance of disabusing parents of such prejudices in the treatment of the child's constipation. Mac Keith (1955), Reichert (1955) and James (1955) all stress the need to emphasize to parents the wide range of normality in bowel function during infancy in order to avoid their unwarranted alarm. In the present series, the longest period of absolute constipation through resistance to defaecation was 83 days (Case 2), during which time the child, aged 3, continued to enjoy perfectly good health and remained symptom-free, eating normally and showing abundant energy throughout. Swenson (1953) reports a similar example of a child who had no bowel movement for eight months, without adverse repercussions.

In any case, some children show a constitutional tendency to infrequent bowel action, dating from the neonatal period. In the present series, there were three examples of this tendency. In each case, the mother had misinterpreted the condition as one of constipation with resulting undue concern and correspondingly rigorous treatment. Significantly, however, although the parental attitude has now been corrected and the overlying behaviour disturbance completely resolved, the child's pattern of bowel action in each case has remained unchanged, with a

bowel movement occurring at three- to five-day intervals. No harm results in such cases unless the child is treated for supposed constipation.

Much depends upon the orientation of the paediatric specialist, since it is to him that the majority of cases of this kind will be referred in the first instance because of their physical presentation. Chapman and Loeb (1955) aptly comment, 'The ultimate success of referral for psychiatric opinion depends upon the referring paediatrician's skill in allaying parental guilt and anxiety about seeking such help. His ability to explain the importance of emotional factors is itself an important factor in whether parents will actually follow up the suggestion of psychiatric referral. A small amount of extra time devoted by the paediatrician in talking to parents about these gastro-intestinal problems, and how life stresses and personality factors affect the ailment, is often one of the most therapeutic things he does. It is often useful to remember that the word "doctor" derives from the Latin verb "docere" —"to teach"!'

Summary and Conclusions

Each of the 30 cases described in the current study, despite their diversity of background, had in common the factor of conflict between parent and child in the sphere of bowel function. Parental efforts to promote bowel regularity had induced a reactive state of negativism in the child, manifested as resistance to defaecation. This in turn led to chronic faecal retention, with ultimate dilatation of the rectum and terminal colon if the condition was allowed to persist for a sufficient length of time. The megacolon so produced could not be attributed to any underlying organic lesion. On the evidence presented, it is of psychogenic origin and is of common origin with the condition sometimes called idiopathic megacolon.

The conclusion drawn from the current investigation is that, while colonic inertia forms the immediate basis of the condition, its development is secondary to the state of chronic constipation which results from persistent bowel negativism.

Rational treatment of the condition should therefore be directed towards resolving the child's negativistic behaviour, since this represents the ultimate basis of the disorder. Treatment must include exploration of the emotional factors within the parent/child relationship which determine the patient's negativistic response, and appropriate re-alignment of parental attitude so that the state of conflict over bowel function is removed.

Joint consultation between paediatrician and child psychiatrist ensures that such a comprehensive approach is instituted. Parental reassurance is thereby more effectively promoted, continuity in treatment is preserved, and, although the physical symptoms are viewed with detachment, there is no risk of neglecting the local bowel disorder while pursuing the broader treatment indications. The paediatrician gains insight into the emotional dynamics of the condition and the psychiatrist gains perspective upon its physiological aspects. Each discipline reinforces the contribution of the other, and the prognosis for successful treatment is thereby enhanced.

It is a pleasure to record my thanks to Professor N. B. Capon for his unfailing interest in this work and for his kindness in providing the facilities within the Department of Child Health of the University of Liverpool which made the project possible. I would also like to thank my colleagues, Miss M. E. Gurney and Dr. W. E. Robinson, for their invaluable help with the therapeutic work; my Psychiatric Social Worker, Miss E. Ireland, for her important contribution in compiling the control group data; our Senior Clinical Psychologist, Mr. John Graham White, for his help with the statistical work; my paediatric colleagues, and in particular Dr. Hudson, Dr. Keidan, Dr. Llewellin and Dr. Todd, for their close collaboration and for their courtesy in providing access to their wards; and to my two secretaries for their industry and patience. Above all I would like to express my deep appreciation to Professor W. Mayer Gross for his support, encouragement and inspiring stimulus.

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BRITISH PAEDIATRIC ASSOCIATION

Proceedings of the Twenty-ninth Annual General Meeting

The Annual Meeting of the British Paediatric Association was held at the Old England Hotel, Windermere, from April 23 to 26, 1958.

BUSINESS PROCEEDINGS. Dr. K. H. Tallerman, M.C., took the Chair as President, and the following members were present:

F. M. B. Allen, E. C. Allibone, I. M. Anderson, J. Apley, Cécile Asher, R. Astley, H. S. Baar, T. E. D. Beavan, M. Bodian, R. E. Bonham Carter, J. V. Braithwaite, P. T. Bray, E. G. Brewis, F. S. W. Brimblecombe, R. W. Brookfield, W. A. B. Campbell, W. H. Cant, N. B. Capon, I. A. B. Cathie, N. S. Clark, T. Colver, W. R. F. Collis, Beryl Corner, S. D. M. Court, John Craig, J. O. Craig, W. S. Craig, Mildred Creak, J. Crooks, W. E. Crosbie, K. W. Cross, Mary Crosse, G. Davison, E. F. Dott, A. C. Doyne Bell, S. Doxiadis, J. L. Emery, P. R. Evans, H. L. Ellis, J. W. Farquhar, J. O. Forfar, Isabella Forshall, A. White Franklin, D. Gairdner, W. Gaisford, W. H. Galloway, R. R. Gordon, S. Graham, C. F. Harris, E. W. Hart, J. Hart-Mercer, C. C. Harvey, J. D. Hay, J. L. Henderson, W. Henderson, A. Holzel, F. P. Hudson, J. H. Hutchison, R. S. Illingworth. J. Jacobs, N. M. Jacoby, Ursula James, H. Jolly, H. Everley Jones, F. F. Kane, J. J. Kempton, G. M. Komrower, R. C. Lightwood, J. Lorber, P. MacArthur, R. A. McCance, D. MacCarthy, Agnes MacGregor, M. MacGregor, R. Mac Keith, T. P. Mann, R. Mayon-White, R. A. Miller, F. J. W. Miller, A. V. Neale, G. H. Newns, D. N. Nicholson, A. P. Norman, J. N. O'Reilly, C. G. Parsons, W. W. Payne, C. Pinckney, P. E. Polani, C. T. Potter, K. B. Rogers, A. Russell, L. Scott, R. A. Shanks, W. Sheldon, Ursula Shelley, Victoria Smallpeice, W. C. Smallwood, J. M. Smellie, J. Forest Smith, T. Stapleton, J. Thomson, M. L. Thomson, J. P. M. Tizard, R. McL. Todd, W. Walker, A. G. Watkins, Cicely Williams, Mary Wilmers, B. D. R. Wilson, D. W. Winnicott, Winifred Young, S. Yudkin.

Professor Bo Vahlquist (Windermere Lecturer) and Mr. G. J. Piller were the guests of the Association.

The following were present as guests of members of the Association:

E. Aberdeen, Charlotte Anderson, J. Baden-Daintree, R. Berg, M. F. G. Buchanan, Bera Buhrmann, Joyce Burke, E. D. Burnard, Joan M. Cashman, C. L. Chen, P. Clay, B. L. Coles, Christine Cooper, J. G. A. Davel, W. Dickson, J. H. Diggle, E. E. Doyle, D. Garrow, S. Griffin, A. D. M. Jackson, Margaret Jones, A. C. Kirby, K. M. Laurence, R. Llewelyn Davies, D. Macaulay, A. E. McCandlass, W. J. Matheson, Florence Mayer, J. Olsen, A. W. M. Page, F. Puga, A. Rigg, H. Rischbieth, S. Sjölin, Jean Smellie, F. H. Stone, G. Weston, D. Whitehouse, T. Wright.

The Annual General Meeting was held on April 24, 1958.

The Minutes of the last meeting, which had been published in the *Archives of Disease in Childhood*, were received and approved.

ELECTION OF OFFICERS. The following were elected:

PRESIDENT: Dr. J. Forest Smith.
PRESIDENT-ELECT: Dr. R. C. Lightwood.
TREASURER: Professor A. G. Watkins.
SECRETARY: Dr. P. R. Evans.

EXECUTIVE COMMITTEE, 1958-61:
Dr. J. Apley, Dr. D. V. Hubble, Dr. P. MacArthur, Dr. L. G. Scott, Dr. E. W. Hart (1958-59).

ELECTION OF MEMBERS. The following were elected:

HONORARY MEMBERS

Dr. K. H. Tallerman, Dr. H. S. Baar, Dr. Frances Braid, Professor C. Dent, Dr. A. G. Ogilvie, Dr. T. Pearse Williams.

CORRESPONDING MEMBERS

Professor S. T. Achar (Madras), Dr. R. C. Eley (Boston), Dr. A. Hartman (St. Louis), Professor D. B. Jelliffe (New Orleans), Professor E. Kerpel-Fronius (Pecs, Hungary), Dr. A. B. Sabin (Cincinnati).

ORDINARY MEMBERS

A. G. V. Aldridge, G. C. Arneil, A. D. Barlow, R. G. G. Barry, T. Bowlby, T. A. Brand, J. Coates, Christine E. Cooper, E. C. R. Couper, M. E. Disney, H. G. Farquhar, H. V. L. Finlay, B. Gans, I. H. Gosset, Gwyn R. Griffith, Sylvia K. Guthrie, T. B. Heycock, C. J. Hodson, R. Jenkins, C. W. Kesson, A. M. MacDonald, R. G. Mitchell, C. Newman, A. P. M. Page, L. J. Prosser, P. P. Rickham, T. S. Rodgers, J. M. Stansfeld, W. P. Sweetman, P. N. Swift, D. H. Wallace, H. R. E. Wallis, C. B. M. Warren, I. G. Wickes, D. A. J. Williamson, B. S. B. Wood, Barbara Woodhead.

The Treasurer's report was received and adopted and the auditors were re-appointed for a further

year. The thanks of the Association were expressed to Dr. R. Lightwood at the expiry of his 11 years' work as Honorary Treasurer.

The report of the Executive Committee was received and approved and is printed below. It was agreed that next year's report should include the names of members of committees. Following a suggestion made by Dr. Beryl Corner it was agreed that the Executive Committee should arrange for more prolonged discussion on paediatric policy, either at the Annual General Meeting or at a special meeting held at another time during the year.

A proposal to alter Rule 15 to read:

'The subscription payable by ordinary members shall be fixed from time to time by the Executive Committee and reported to the members of the Association',

was referred back to the Executive Committee for further consideration.

There was considerable discussion of an offer by the Journals Committee of the British Medical Association to allow members of the Association to receive the *Archives of Disease in Childhood* at a reduced rate of subscription provided that virtually all members subscribed. On a show of hands the following resolution was passed by 42 votes to 37: 'That the Executive Committee should consider consolidating the subscription to the Association and to the *Archives of Disease in Childhood*'.

Report of the Executive Committee 1957-58

1. We note with sorrow the death of four original members, Dr. A. G. Maitland Jones, Dr. Wilkie Scott, Dr. William Brown and Dr. H. C. Cameron.

2. We congratulate Professor A. A. Moncrieff on his election to fellowship of the Royal College of Obstetricians and Gynaecologists, and Dr. C. F. Harris on his nomination as Vice-Chancellor of the University of London.

3. Reports and Committees. The report on hospital accommodation for children was published in the *Lancet* in July, 1957. The report of the Child Psychology Committee on child guidance has been submitted to the Ministry of Health. Written evidence has been submitted to the Platt Committee on the welfare of children in hospital. At the request of the Ministry of Agriculture, Fisheries and Food draft regulations on soft drinks have been studied in relation to child health and comments have been submitted. A Committee has been set up to consider paediatric care in infectious diseases hospitals and sanatoria, and another to discuss the medical care of adolescents. The Joint Committee on Prematurity has been replaced by a Standing Joint Committee of the British Paediatric Association and Royal College of Gynaecology, which will consider matters of common interest.

4. Meetings. It will be impossible to hold future meetings in Windermere and the Executive recommends that in 1959 the Annual General Meeting should be held at the Royal Hotel, Scarborough. The Canadian Paediatric Society has suggested having a joint meeting with us in Britain in 1961, and it is proposed that it shall replace our usual annual meeting in that year.

5. Diploma of Child Health. Regulations for the D.C.H. demand from clinical assistants four attendances a week. In order to encourage general practitioners to take the examination the Conjoint Board has been asked to approve less frequent attendance over a longer period and has agreed to do so.

6. Children in Adult Wards. One of the main topics for discussion during the past two years has been the question of how many children who could be nursed in children's wards are admitted to adult wards. Further information is being collected: there appears to be much regional variation.

7. Windermere Lecture. Professor Bo Vahlquist (Uppsala) delivered the Windermere Lecture entitled 'Breast milk and cow's milk in infant feeding: a clinical, serological and biochemical study in 400 children'.

Scientific Sessions

Ursula James (London). 'The Diagnosis of Urinary Infection in the Newborn.' Observations on the incidence and diagnosis of urinary infections in the newborn have been made over a period of one year in a maternity unit of 65 beds. The clinical picture and urinary investigations have been analysed, and the results compared with similar investigations in 100 normal infants. The value of actual white cell counts in the urine has been investigated, and a range of cell counts in normal infants has been compared with those found in patients with urinary infections. Suggestions are offered for making early and more certain diagnosis of infections of the urinary tract in the newborn.

W. S. Craig and M. F. Buchanan (Leeds). 'Hypocalcaemic Tetany on the Second Day of Life.' To be published in full.

F. H. Stone (Glasgow). 'Infantile Autism.' The clinical features of infantile autism (Kanner's syndrome), based on the intensive study of several cases, were described and illustrated by means of a cine-film. Aetiological factors were considered and an experimental therapeutic approach described. Suggestions were made as to future lines of research.

G. M. Komrower (Manchester). 'Sequelae of Infantile Renal Acidosis.' To be published in full.

W. GAISFORD (Manchester). 'Poliomyelitis Vaccination of Newborn Infants.' Groups of newborn infants were given poliomyelitis vaccine and their titres examined to see if maternally transmitted antibodies inhibited the natural development of antibodies after vaccination and whether triple negative infants would produce reasonable titres. The effect of a booster dose seven to eight months later was also investigated.

D. GAIRDNER (Cambridge). 'The Fluid Shift from the Vascular Compartment Immediately after Birth.' To be published in full.

K. M. LAURENCE (London). 'The Natural History of Hydrocephalus.' It is generally believed that, untreated, few children with hydrocephalus survive and that those who do survive are doomed to permanent institutional care. Nearly 200 cases of untreated hydrocephalus, seen by Mr. Wylie McKissock (who rarely operates upon this condition) since 1939, have been followed up. Forty-six per cent of the series have survived with the hydrocephalus spontaneously arrested. These have been re-examined and intelligence tested. Many of those who showed evidence of spasticity and incoordination in infancy have now no 'motor trouble', and on intelligence testing 44% fall within the 'average' group (I.Q. of 85 and above). A further 20% are educable with an I.Q. of above 50, leaving only 25% requiring complete institutional care. Thirty-five per cent of the survivors are growing up as completely normal individuals, both physically and mentally. Children with acquired hydrocephalus, generally due to a basal cistern block, bore the most hopeful prognosis.

In the light of this a more hopeful approach to this condition is called for, in spite of the fact that the disease often causes some brain damage, and that mental development in many cases is temporarily delayed in the early years.

I. A. B. CATHIE (London). 'On Editing the Archives.' The general functions of an editor and his responsibility to contributors and readers were briefly considered and the experience of nine years editing the *Archives of Disease in Childhood* was analysed. The types of articles submitted for publication were considered, the reasons for rejections given and the principles involved in the editing of accepted papers were discussed. Common discordances in the construction of papers and the presentation of results were outlined, as were some of the commoner grammatical extravagances. Finally, an attempt was made to indicate the type of paper most likely to give the maximum information in the minimum space and require the least amount of alteration and therefore be most acceptable.

CHRISTINE E. COOPER and S. GRIFFIN (Newcastle). 'Oesophageal Stricture Secondary to Hiatus Hernia.' An account was given of 18 cases seen since 1952 during a study of hiatus hernia in 356 infants. The age range was 2 months to 12 years when first seen. Stricture was already present at the first visit in 15. Many had been previously treated as behaviour problems. Details of history and clinical diagnosis were presented. The importance of an experienced radiologist and careful technique during barium studies was emphasized. A preliminary account of conservative management in 15 and radical surgery in three, description of complications and emphasis on need for long-term study were given.

A. D. M. JACKSON and L. FISCH (London). 'Deafness following Maternal Rubella: Results of a Prospective Survey.' Detailed clinical examinations and hearing tests (including audiograms) were carried out on a series of 57 children, whose mothers were known to have had rubella during the first 18 weeks of pregnancy. Fifty-seven controls were also examined.

The children were taken from the records of the national prospective enquiry into the effects of virus infections in pregnancy organized by the Society of Medical Officers of Health and the Ministry of Health.

A preliminary report of the findings of this investigation was presented. The results will be published in full elsewhere.

JEAN SMELLIE (London). 'The Effect on the Infant of Large Therapeutic Doses of Vitamin D given to the Mother throughout Pregnancy.' The clinical and biochemical follow-up were described on two infants now aged 6 months and 2 years, born to a mother suffering from severe Type I renal tubular osteomalacia. She had been successfully treated with A.T. 10 for six months before the first pregnancy and received pure dihydrotachysterol throughout both pregnancies (1 mg. o.d. by mouth).

Both infants showed biochemical signs of mild vitamin D intoxication, namely a low plasma alkaline phosphatase and a slightly raised serum calcium followed by a rise of blood urea.

Lactation was suppressed in each case. In the first, the infant was fed on National Dried Milk and between 2 and 3 months became hypotonic with increased reflexes. These signs disappeared when the National Dried Milk was replaced by liquid cow's milk. The second child, fed on liquid cow's milk from birth, showed no hypotonia.

The implications of these findings were discussed, particularly in relation to the aetiology of idiopathic hypercalcaemia of infancy; for instance, that an infant may be 'sensitized' in utero to vitamin D by an excessive maternal intake of vitamin D during pregnancy in health foods and vitamin capsules.

MALCOLM MACGREGOR (Warwick). 'Osteomyelitis Variolosa.' There is only one account in British literature, in 1887, of this interesting bone complication of smallpox, of which I had the opportunity to study 20 cases in Nigeria last year.

This short paper illustrates the condition, which is radiologically very striking, and draws some parallels with other virus affections of bone, more likely to be in the minds of members of the B.P.A.

BOOK REVIEWS

Comparative Aspects of Haemolytic Disease of the Newborn. By G. FULTON ROBERTS. (Pp. xi+199. 17s. 6d.) London: Heinemann. 1957.

This is an erudite little book, most amusing and interesting in its way and packed full of information. It is very rarely that the clinical, historical, pathological and comparative aspects of a disease are brought together in a single volume, but they are all here and discussed in a simple and readable style. It is not, however, by any means easy reading throughout and this is a book for the clinician who has some knowledge of the problem, or for the pathologist who does not wish to confine himself only to the finer points of serology, rather than the student.

The author has included up to date references and covers the literature fully. Some might find fault with his presentation of the case against premature induction of labour on page 138, but it would be unreasonable to make much of this.

In summary, this is a stimulating approach which might well be copied in respect to other diseases and which should remind many of us how little we know of the wider aspects of those diseases in which we are interested.

Affections Non Congénitales de l'Anus et du Rectum Chez l'Enfant. By JEAN DUHAMEL, with Preface by Professor Robert Debré. (Pp. vii+264; 110 figures. Fr. fr. 3,600.) Paris: Masson. 1958.

This book is based on a study of 450 cases of ano-rectal disorders treated at l'Hôpital des Enfants-Malades à Paris. In the examination of such cases, the author recommends the use of an angulated frame to keep the infant in the jack-knife position. The technique of instrumentation and its dangers are set out.

The cause, clinical features, pathology and treatment of all non-congenital, ano-rectal diseases are given in detail. The solitary polyp (140 cases) and rectal prolapse (90 cases) are the two commonest conditions; anal fissure, peri-anal abscesses and fistulae are fully described. The author's view throughout the book almost completely conforms with current teaching and proctological practice. All minor operative procedures are given in detail. A few points, however, may not receive general acceptance, namely, the use of the blind external route for the sub-mucosal injection of prolapsus ani, the use of a rubber seton in treating fistulae and the injection of antibiotics, after aspiration, into peri-anal abscesses. These procedures are given only as alternatives to the more orthodox methods.

Dr. Duhamel, who was a gastro-enterologist, shows his special interest in the chapters on proctitis, anal inflammation, constipation and encopresis. More rare affections, such as multiple polyposis, malignant and venereal disease, are also included.

This book is well illustrated, mostly by clear line drawings, but a few of the photographs are of poor quality; there is a synopsis of each chapter and a useful bibliography.

The author is to be congratulated on producing this book on proctology in a special age group, for he has made available much useful information for all those called upon to treat these infant and childhood disorders. It is unfortunate that malformations and neonatal affections do not come within the scope of this book. Perhaps this omission can be remedied in a second edition.

Hydrocéphalie du Nourrison. By MARC RICHARD KLEIN. (Pp. 136; 37 figures. Fr. fr. 1,600) Paris: Masson. 1958.

This monograph of 133 pages attempts to deal with the whole problem of hydrocephalus as well as the physiology of the cerebrospinal fluid circulation. Unfortunately, it manages only to skate over the subject without giving precise data or references.

The 'classification' given merely lists tumours and lesions which may lead to hydrocephalus, and confuses rather than clarifies the problems. Investigation of such cases is dealt with in some detail, including the use of isotopes, which are, as yet, a research tool of only doubtful value. The clinical examination, however, is added as a postscript in a few lines at the end of the chapter.

Several operations are described, notably that of coagulation of the choroid plexus, which is the author's chief tool in combating the malady. Anaesthesia and post-operative problems are discussed at length.

Some of the diagrams are clear, though often irrelevant; others are confusing, while the clinical photographs are unhelpful, especially one of a hydrocephalic baby wearing a bonnet.

The impression gained from this monograph is that the author has compiled it at some speed without giving any deep thought to the problems involved.

Pseudarthrose Congenitale du Tibia et son Traitement. By M. GUILLEMINET and R. RICARD. (Pp. 98; 78 figures. Fr. fr. 1,800) Paris: Masson. 1958.

This is a review of the pathogenesis and treatment of congenital pseudarthrosis of the tibia, and is based upon a review of the literature and 14 personal cases of the author. Since three of these cases are too recent for assessment, and most of the others have already been reported elsewhere, it is difficult to appreciate the issue of this material in book form. The experience of the authors in the treatment of this condition lies largely in the field of inlay and sliding grafts to the tibia, with which they have had considerable success, but the bypass graft and the use of an intramedullary nail are also fully described. In such a beautifully produced book it is a pity that the bibliography is not complete, and contains minor inaccuracies.

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